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(54) Anti-inflammatory/anti-allergic compounds.

(57) Compounds of the formula:



and salts thereof,
wherein

Ar₁ is a nitrogen, sulfur, oxygen heterocyclic ring or aromatic ring;

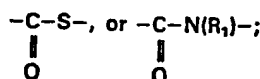
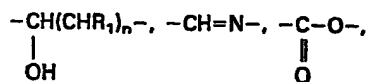
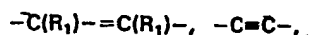
Ar is a phenyl ring or a nitrogen, oxygen or sulfur heterocyclic ring;

Ar and Ar₁ may be fully substituted or less than fully substituted with H, CH₃, lower alkyl, aryl, aralkyl, halo, hydroxy, lower alkoxy, CF₃, carboxy, alkylcarboxy, arylcarboxy, alkylcarbalkoxy, alkanoyl, formyl, oxo, nitrilo, amino, aminoalkyl, alkylamine, carboxamide, aryloxy, nitro, sulfonyl, sulfonamide, thio, or alkylthio;

X = -O(CHR₁)_n-, -S(CHR₁)_n-, -NR₂(CHR₁)_n-alkylene



of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms,



Z is an alkylene chain containing up to 10 carbon atoms in the principal chain and a total of up to 12 carbon atoms and from 0 to 2 double bonds and the said alkylene chain may be attached to Ar through an oxygen, sulfur or amino nitrogen atom, and when n'=2, one of the R substituents may be halogen on an omega carbon of the alkylene chain Z; when n'=1, R is a substituent attached to one of the carbon atoms of Z selected from the group consisting of =O, OR₃, SR₃, N(R₂)₂ and R₁, -COR₄ and when n'=2 one R is previously defined and the additional R is a substituent attached to one of the carbon atoms of Z selected from the

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group consisting of =O, OR₃, SR₃, N(R₂)₂, -COR₄, lactone and halo;

R₁ is H or CH₃;

R₂ is H, lower alkyl, aryl or aralkyl;

R₃ is H, lower alkyl, lower alkanoyl, aryl, aralkyl or substituted aryl in which the substituent is halo, lower alkyl or lower alkoxy;

R₄ is OR₂ or N(R₂)₂;

n = 0 or 1;

n' = 1 to 7; and

n'' = 0, 1 or 2.

2. A compound of the formula:



and salts thereof,

wherein

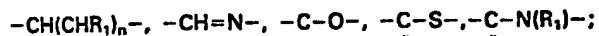
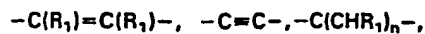
Ar₁ is quinolyl;

Ar is a phenyl, pyridyl or quinolyl ring;

X = -O(CHR₁)_n-, -S(CHR₁)_n-, NR₂(CHR₁)_n-, alkylene



of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms,



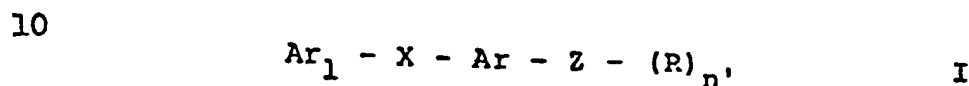
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1 ANTI-INFLAMMATORY/ANTI-ALLERGIC COMPOUNDS

This invention relates to new chemical compounds possessing valuable pharmaceutical activity. More particularly, the invention relates to novel lipox-
 5 genase inhibitor compounds possessing anti-inflammatory and anti-allergic activities.

The present new compounds are of the formula:

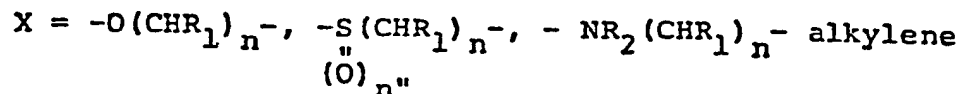


and salts thereof,

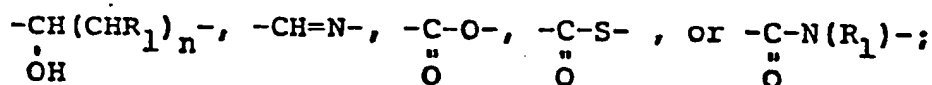
15 wherein

Ar_1 is a nitrogen, sulfur or oxygen heterocyclic ring or an aromatic hydrocarbon ring such as phenyl, naphthyl, phenanthryl or anthryl;

20 Ar is a phenyl ring or a nitrogen, oxygen or sulfur heterocyclic ring;



25 of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms, $-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-$, $-\text{C}\equiv\text{C}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}(\text{CHR}_1)_n-$,



30

35

1 Z is an alkylene chain containing up to 10
carbon atoms in the principal chain and a total of up
to 12 carbon atoms and from 0 to 2 double bonds and
the said alkylene chain may be attached to Ar through
5 an oxygen, sulfur or amino nitrogen atom, and when
n'=2, one of the R substituents may be halogen on an
omega carbon of the alkylene chain Z;

 when n'=1, R is a substituent attached to
one of the carbon atoms of Z selected from the group
10 consisting of =O, OR₃, SR₃, N(R₂)₂, R₁ and -COR₄, and when
n'=2 and R is as previously defined and the additional
R is a substituent attached to one of the carbon
atoms of Z selected from the group consisting of =O,
15 OR₃, SR₃, N(R₂)₂, -COR₄ and halo;

 R₁ is H or CH₃;
 R₂ is H, lower alkyl, aryl or aralkyl;
 R₃ is H, lower alkyl, lower alkanoyl, aryl,
aralkyl or substituted aryl in which the substituent
is halo, lower alkyl or lower alkoxy;

20 R₄ is OR₂ or N(R₂)₂;
 n = 0 or 1;
 n' = 1 to 7; and
 n'' = 0, 1 or 2.

 In the foregoing description, the lower alkyl and
25 alkanoyl groups contain up to 6 carbon atoms which may be in
the normal or branched configuration, including methyl,
ethyl, propyl, isopropyl, butyl, isobutyl, amyl, isoamyl,
hexyl, and the like. The aryl group is preferably phenyl,
and aralkyl is benzyl. The alkanoyl group is preferably
30 acetyl.

1 As employed herein, the expression "nitrogen,
sulfur or oxygen heterocyclic ring" is meant to include
those heterocyclic rings which include at least one sul-
fur, nitrogen or oxygen atom, but which may include one
5 or several of the said atoms. This expression also is
intended to include the so-called "benzo" heterocyclics.
Representative heterocyclic rings include furan, thiophene,
pyrrole, pyridine, pyrazine, thiazole, oxazole, quinoline,
indole, benzothiophene, benzofuran, benzoxazole and the like,
10 as well as N-oxides of the nitrogen heterocyclics.

Ar is preferably a monocyclic ring, e.g., phenyl,
pyridine, thiophene, furan and pyrrole, while Ar₁ in one
embodiment is preferably a bicyclic nitrogen, oxygen or
sulfur heterocyclic ring, e.g., quinoline, indole, benzo-
15 furan and benzothiophene and in another embodiment is
preferably a monocyclic or bicyclic non-heterocyclic ring,
e.g. phenyl or naphthyl. These rings are attached in their
respective positions in the molecule of the present new
compounds through any available carbon of the ring, but
20 preferably through the 2-position of Ar₁.

Ar and Ar₁ may be fully substituted or less than
fully substituted, e.g. mono- or di- or tri- or tetra-
substituted with a variety of substituents such as H, CH₃,
lower alkyl, aryl, aralkyl, halo, hydroxy, lower alkoxy,
25 CF₃, carboxy, alkylcarboxy, arylcarboxy, alkylcarbalkoxy,
alkanoyl, formyl, oxo, nitrilo, amino, aminoalkyl, alkyl-
amine, carboxamide, aryloxy, nitro, sulfonyl, sulfonamide,
thio or alkylthio. It is preferred that the said substituents
be present in intermediate compounds used in forming the
30 final products as described in the disclosure of methods of
preparation which follows. The substituents may be
present on any of the available positions of the ring

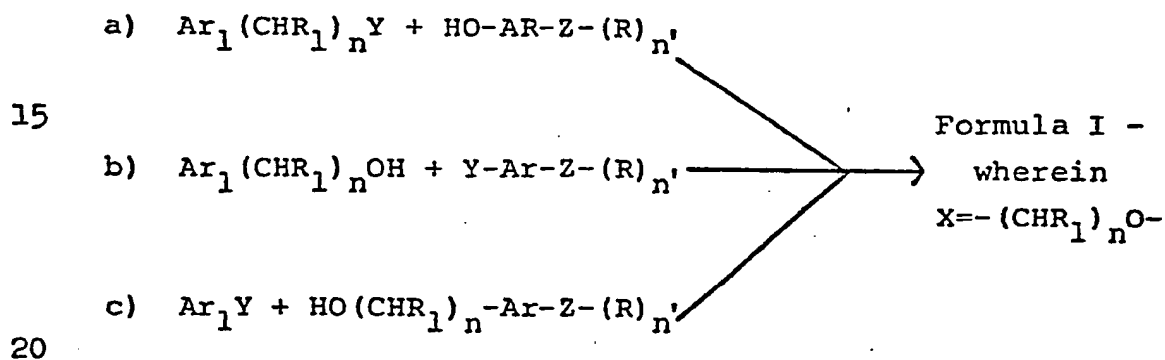
- 1 systems representative of Ar and Ar₁. Of course, substituents which are reactive under the synthetic conditions employed should be blocked using appropriate blocking groups which are readily removable after formation of the
5 desired products. Such blocking groups are well known to those skilled in this art.

The alkylene chains represented by Z can be normal or branched chains in which the branches are preferably methyl or ethyl and include those in which two such groups, e.g., methyl, are on the same carbon atom. The alkylene chains preferably contain up to 8 carbon atoms whether branched or normal. The alkylene chain may contain up to 2 double bonds
15 and may be attached directly to the Ar ring through an oxygen, sulfur or amino nitrogen atom. In addition to substituent R, which is attached to one of the carbon atoms as depicted in the foregoing formula, other substituents such as halogen (F, Cl, Br or I)
20 can be present on the alkylene chain, particularly on the terminal carbon.

Of the various groups representative of X in the foregoing formula, the preferred are those in which $n = 1$, and especially those which include an oxygen
25 function, particularly the group $-O(CHR_1)_n-$ in which n is 1 and R_1 is H. The disposition of the said groups between Ar and Ar₁ is not critical, e.g., the $-O(CHR_1)_n-$, can be attached with the oxygen directly on Ar₁ or on Ar. Preferably, the oxygen of $-O(CHR_1)$ is attached
30 to Ar₁.

- 1 In the most preferred compounds of this invention, Ar is
phenyl, Ar₁ is 2-quinolyl, phenyl or naphthyl, X is
-OCH₂-, Z is alkylene of from about 5-8 carbon atoms
and R is an oxygen-containing group, preferably,
5 hydroxy, and n' is 1.

The present new compounds can be prepared
by art-recognized procedures. For compounds in which
X = -O(CHR₁)_n, any of the standard ether forming
reactions can be employed as illustrated by the
10 following general procedures:



In these modifications, Y is a leaving group,
most commonly halogen, preferably Cl, Br or I, which forms
HY with the hydrogen of the alcohol. Illustrative of
25 processes a) and b), 2-chloromethylquinoline or chloro-
methylbenzene is condensed with 1-(3-hydroxyphenyl)-1-
pentanol and 2-hydroxymethyl-quinoline or hydroxymethylbenzene
is condensed with 1-(3-bromophenyl)-1-pentanol. Illustrative
of process c) is the condensation of 2-bromopyridine or
30 bromobenzene with 5-(1-hydroxyhexyl) furfuryl alcohol to form
the corresponding pyridyl-furylmethyl ether or phenyl-
furylmethyl ether. Alternatively,

1 the leaving group can be a sulfonate ester group,
such as the tolyl sulfonate group, which forms toluene-
sulfonic acid with the hydrogen of the OH group.
In all cases where an acid is the by-product, it is
5 preferred to use an acid acceptor to neutralize the
acid in the reaction mixture. Such acid acceptors
are well-known in the art and include various alkali
and alkaline earth metal carbonates and bicarbonates,
e.g., sodium carbonate, potassium bicarbonate, cesium
10 carbonate and like, alkali metal alkoxides such as
sodium ethoxide, potassium ethoxide and the like,
as well as organic amines such as pyridine, pyrrole,
dimethylamine, and similar such amines. Of course,
when Ar₁ and/or Ar includes a basic nitrogen hetero-
15 atom, this can serve as the acid acceptor and the pro-
duct is obtained as an acid salt.

To form compounds in which X is $\begin{matrix} -S(CHR_1)_n \\ \text{"O"}_n \end{matrix}$

20 the same reactions can be used employing the corre-
sponding mercaptans in lieu of the alcohols. The
sulfoxides and sulfones (where n" = 1 or 2) can be
formed by the known reaction with peroxides such as
hydrogen peroxide or benzoylperoxides.

25 For compounds in which X is $-NR_2-(CHR_1)_n-$,
the corresponding amino starting compounds are employed
to form the desired amino compound. Thus, 2-aminopyridine
is condensed with 3-(1-hydroxyhexyl)benzylbromide to
form 2-[3-(1-hydroxyhexyl)benzylamino]pyridine. Alter-
30 natively, 2-quinolylmethylbromide is condensed with
3-(1-hydroxyhexyl)aniline to form 2-[3-(1-hydroxyhexyl)
anilinomethyl]quinoline. Aniline is condensed with
3-(1-hydroxyhexyl)benzylbromide to form 2-[3-(1-hydroxy-
hexyl)benzylamino]benzene and benzyl bromide is condensed
35 with 3-(1-hydroxyhexyl)aniline to form 2-[3-(1-hydroxyhexyl)
anilinomethyl]benzene.

1 Compounds in which X is -CH=N- are so-called
 anils and are prepared by condensing an aldehyde with
 the corresponding amine. Thus, 2-aminopyridine can be
 condensed with 5-(1-hydroxybutyl)furfural to form the
 5 corresponding anil. Alternatively, thiophene-2-
 aldehyde can be condensed with 5-(1-hydroxypentyl)
 pyrrolylmethylamine to form the corresponding anil.
 Aniline can be condensed with 5-(1-hydroxybutyl)furfural
 to form the corresponding anil and thiophene-2-aldehyde
 10 can be condensed with 5-(1-hydroxypentyl) benzylamine to
 form the corresponding anil.

For those compounds in which X is $\begin{array}{c} \text{-C-O-} \\ \parallel \\ \text{O} \end{array}$,

15 $\begin{array}{c} \text{-C-S-} \\ \parallel \\ \text{O} \end{array}$ or $\begin{array}{c} \text{-CNR}_1- \\ \parallel \\ \text{O} \end{array}$, the acid Ar_1COOH is esterified with
 HO-Ar-Z(R)_n , or the corresponding mercaptans, and
 the amide is formed by reaction of a suitable derivative
 of the acid with the amine, $\text{HNR}_1\text{Ar-Z(R)}_n$. Since
 20 the group -Z(R)_n may contain a group reactive with the
 aforesaid acid derivatives, it is preferred that the
 desired group -Z(R)_n be formed after the acylation
 reaction is completed. This can be accomplished by
 providing a group convertible to the desired group
 25 in the Ar nucleus. Such convertible groups include,
 for example, the nitrilo and formyl groups, which
 after acylation, can be converted to aminoalkyl in

1 the case of the nitrilo group or to hydroxyalkyl in
the case of the formyl group, e.g., by reaction with
a Grignard reagent to form a secondary alcohol of any
desired carbon length. The position of the amino
5 or alcohol hydroxy groups can be set by merely selecting
the length of carbon chain (where present) separating
the nitrilo or formyl group from the Ar ring carbon
as should be obvious to those skilled in the art.

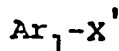
Of course, the group $-Z(R)_n$, may contain groups
10 which are non-reactive in formation of the X linkage
between Ar and Ar_1 and such groups as are non-reactive
may be present on the Ar nucleus before such formation,
e.g., ether groups such as alkoxy, alkylmercapto, phenoxy,
and the like, keto-carbonyl, alkoxy-carbonyl and car-
15 boxamido groups. After formation of the X-linkage,
such non-reactive groups can be converted to
 1° , 2° or 3° alcohol groups by reduction of a
carbonyl or reaction with a Grignard reagent with
the carbonyl or by reduction of an ester group, $COOR_4$.

20 For compounds in which Z is ethylenic,
 Ar_1CH_2Y is condensed with $R_1\overset{\overset{O}{\parallel}}{C} - ArZ(R)_n$, to form the
desired ethylenic compound. From those in which R_1 is
H, the corresponding acetylenic compounds can be
25 obtained by halogenation to form the dihalo compound
and dehydrohalogenation to remove 2 equivalents of
hydrogen halide.

Thus, the compounds of the present invention can
30 be prepared by various synthetic methods as exemplified by
the following:

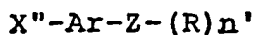
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- 1 1. Condensation of a compound of formula II



II

- 5 in which X' is $-\text{CH}_2\text{Hal}$, Hal, OH, CH_2OH , SH, or CH_2SH ;
with a compound of formula III



III

- 10 in which X'' is $-\text{CH}_2\text{Hal}$, Hal, OH, CH_2OH , SH or CH_2SH ,
through elimination of X' and X'' with a residue Z remaining
after condensation. Such condensation reactions are known
and occur between, for example, $-\text{CH}_2\text{Hal}$ and -OH with the
elimination of hydrogen halide and formation of the
15 bridging group $-\text{CH}_2\text{O}-$ between the two rings of the resulting
product. Substituting simply halogen in place of $-\text{CH}_2\text{Hal}-$
results in the diphenyl ether structure (where X is -O-).
This reaction is known as Ullman ether synthesis.
Substituting the analogous sulfuric intermediates provides
20 the sulfur analogs of the aforesaid compounds (where X
is -S- or $-\text{CH}_2\text{S}-$).

A variation of this synthetic route employs the
Grignard reagent in place of the halogen-containing sub-
stituent.

- 25 2. When X is unsaturated hydrocarbyl $[-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-$
or $-\text{C}\equiv\text{C}-$, a compound of formula II in which X' is vinyl
or acetylenyl is condensed with a compound of formula III
in which X'' is halogen, usually in the presence of an
active metal (Na, Li, etc.). Alternatively, X' and X''
30 of course can be reversed, i.e., X' can be halogen and
X'' the unsaturated hydrocarbyl group.

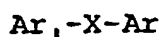
1 3. When Z is -CH=N-, X' and X" can be -CHO
and NH₂ and anil formation will result in production of
the final product.

5 4. When Z is an amide or ester linkage, i.e.,
-COZ-, X' and X", of course, are COOH, and OH or NH on
either formula II or formula III, by classical ester or
amide formation methods.

10 5. When Z is a carbonyl, i.e., C=O, X' and
X" are H and an acylating group on either formula II or
formula III by classical ketone formation reaction, e.g.,
by Friedl-Crafts reaction; or alternatively by oxidation
of the compound in which Z is -CHOH-.

15 6. When Z includes -NR₄- by classical methods
of forming diphenyl amines which include reaction between
the compound (either of formula II or III) in which
X' or X" is -NR₄H- with the compound (formula II or III)
in which X' or X" is halogen.

20 7. Alternatively, substituent -Z-(R)_n' can
be added to compounds of formula IV



IV

25 using classical acylation or alkylation condensation reactions,
for example, an acylating derivative of an acid



30 with a Friedl-Crafts catalyst to provide compounds in which



-11-

1 from which compounds in which R is other than O can be prepared by known reactions, e.g., reduction of the carbonyl oxygen to -OH using lithium aluminum hydride and similar reducing agents.

5 Substituents on Ar₁ can be present in the starting intermediates in the foregoing synthetic routes or alternatively can be added by suitable substitution reactions using the starting compounds of formula I herein in which Ar₁ is substituted with hydrogen.

10 The described reactions are performed using classical organic reactions known to those skilled in the art. Of course, reactive groups where present are preferably

15 blocked by known methods to avoid competing or secondary reactions.

 The aforesaid reactions are carried out in an organic solvent for the reactive starting materials at temperatures ranging from room temperature up to the reflux temperature of the reaction mixture. In condensation reactions in which hydrogen halide is formed, a hydrogen halide acceptor, i.e., usually a basic compound such as an organic amine, is present to facilitate the reaction. In those reactions where a Friedl-Crafts catalyst is employed, aluminum chloride or zinc-chloride are generally useful.

25 The final products are recovered from the reaction mixtures and subsequently purified by art-recognized procedures, e.g., column chromatographic techniques.

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1 The compounds of the invention containing
basic nitrogen form salts with acids, both organic and
inorganic acids. Of particular value are salts with
pharmaceutically-acceptable acids especially in dosage
5 forms predicated on aqueous systems where the enhanced
water solubility of the salts is most advantageous.
Salts formed with pharmaceutically unacceptable acids
are also useful in the isolation and purification of
the basic nitrogen-containing present new compounds.
10 Salts include those formed with hydrochloric, sulfuric,
nitric, perchloric, benzenesulfonic, toluenesulfonic,
phosphoric, acetic, malic, malonic, tartaric and
similar such acids.

 The compounds of the invention also exist
15 in stereoisomeric forms due to the presence of
asymmetric centers in the molecule, especially in the
group $-Z(R)_n$, and in the linkage $-X-$ (where R_1 is other
than H) or in other parts of the molecule. This inven-
tion contemplates the stereoisomers individually or in
20 mixtures or as the racemic compound. The individual
stereoisomers can be obtained by standard resolution
procedures known to those skilled in the art or by
stereospecific synthesis.

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1 The compounds of the present invention can be
administered to the host in a variety of forms adapted to
the chosen route of administration, i.e., orally, or
parenterally. Parenteral administration in this respect
5 includes administration by the following routes: intravenous,
intramuscular, subcutaneous, intraocular, intrasynovial,
transepithelially including transdermal, ophthalmic,
sublingual and buccal; topically including ophthalmic,
dermal, ocular, rectal and nasal inhalation via insufflation
10 and aerosol and rectal systemic.

 The active compound may be orally administered, for
example, with an inert diluent or with an assimilable edible
carrier, or it may be enclosed in hard or soft shell gelatin
capsules, or it may be compressed into tablets, or it may be
15 incorporated directly with the food of the diet. For oral
therapeutic administration, the active compound may be
incorporated with excipient and used in the form of
ingestible tablets, buccal tablets, troches, capsules,
elixirs, suspensions, syrups, wafers, and the like. Such
20 compositions and preparations should contain at least 0.1% of
active compound. The percentage of the compositions and
preparations may, of course, be varied and may conveniently be
between about 2 to about 60% of the weight of the unit. The
amount of active compound in such therapeutically useful
25 compositions is such that a suitable dosage will be obtained.
Preferred compositions or preparations according to the
present invention are prepared so that an oral dosage unit
form contains between about 50 and 300 mg of active compound.

 The tablets, troches, pills, capsules and the like
30 may also contain the following: A binder such as gum traga-
canth, acacia, corn starch or gelatin; excipients such as
dicalcium phosphate; a disintegrating agent such as corn
starch, potato starch, alginic acid and the like; a lubricant
such as magnesium stearate; and a sweetening agent such as
35 sucrose, lactose or saccharin may be added or a flavoring

1 agent such as peppermint, oil of wintergreen, or cherry
flavoring. When the dosage unit form is a capsule, it may
contain, in addition to materials of the above type, a liquid
5 carrier. Various other materials may be present as coatings
or to otherwise modify the physical form of the dosage unit.
For instance, tablets, pills, or capsules may be coated with
shellac, sugar or both. A syrup or elixir may contain the
active compound, sucrose as a sweetening agent, methyl and
propylparabens as preservatives, a dye and flavoring such as
10 cherry or orange flavor. Of course, any material used in
preparing any dosage unit form should be pharmaceutically pure
and substantially non-toxic in the amounts employed. In
addition, the active compound may be incorporated into
sustained-release preparations and formulations.

15 The active compound may also be administered
parenterally or intraperitoneally. Solutions of the active
compound as a free base or pharmacologically acceptable salt
can be prepared in water suitably mixed with a surfactant such
as hydroxypropylcellulose. Dispersions can also be prepared
20 in glycerol, liquid polyethylene glycols, and mixtures thereof
and in oils. Under ordinary conditions of storage and use,
these preparations contain a preservative to prevent the
growth of microorganisms.

The pharmaceutical forms suitable for injectable use
25 include sterile aqueous solutions or dispersions and sterile
powders for the extemporaneous preparation of sterile
injectable solutions or dispersions. In all cases the form
must be sterile and must be fluid to the extent that easy
syringability exists. It may be stable under the conditions
30 of manufacture and storage and must be preserved against the
contaminating action of microorganisms such as bacteria and

-15 -

- 1 fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils.
- 5 The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of micro-
- 10 antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the
- 15 compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

- Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients
- 20 enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above.
- 25 In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.
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-16-

1 The therapeutic compounds of this invention may
be administered to a mammal alone or in combination with
pharmaceutically acceptable carriers, as noted above, the
proportion of which is determined by the solubility and
5 chemical nature of the compound, chosen route of administra-
tion and standard pharmaceutical practice.

 The physician will determine the dosage of the
present therapeutic agents which will be most suitable
for prophylaxis or treatment and it will vary with the form
10 of administration and the particular compound chosen, and
also, it will vary with the particular patient under treatment.
He will generally wish to initiate treatment with small
dosages by small increments until the optimum effect under
the circumstances is reached. The therapeutic dosage will
15 generally be from 0.1 to 100 μ M/day or from about 0.1 mg to about
50 mg/kg of body weight per day and higher although it may
be administered in several different dosage units. Higher
dosages are required for oral administration.

 The following examples are illustrative.
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-17 -

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EXAMPLE 12-[3-(1-Hydroxy-2-methylhexyl)phenoxy-methyl]quinoline

- A. A solution of the ketone, 2-(3-hexanoylphenoxy-methyl)-quinoline (prepared from 3-hexanoylphenol and 2-chloro-methyl quinoline) (6 g, 0.018 mol) in dry THF (25 ml) was added slowly to a mildly refluxing suspension of sodium hydride (1.3 g, 0.054 mol) in dry THF (75 ml) containing excess methyl iodide (10.3 g, 0.073 mol). After the addition of the ketone was complete (30 min.), the reaction mixture was refluxed for 4 hours. After cooling the mixture to room temperature, excess NaH was destroyed by adding methanol. All volatiles were removed at the rotary evaporator and the residue was taken up in ethyl acetate. The organic extract was washed with water and brine, and dried over anhydrous magnesium sulfate. Upon removal of all solvent, the mono-methylated ketone (2-[3-(2-methylhexanoyl)phenoxy-methyl]quinoline, was obtained as a yellow oil weighing 8 g.
- B. This ketone (8 g) was next reduced with sodium borohydride (1.4 g, 0.036 mol) in ethanol (100 ml) at room temperature for about 15 hours. A little water and methanol was added to the reaction mixture, and then most of the volatiles were removed at the rotary evaporator. The residue was thoroughly extracted with ethyl acetate, and the organics were washed with water, brine, and then dried over anhydrous MgSO_4 . All solvent was removed to leave a yellow oil (6 g) which was chromatographed on silica gel using 20% ethyl acetate in hexane as eluent. The desired mono methylated alcohol was obtained as a yellowish solid (1.5 g), mp. 64-67°C.

-18-

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EXAMPLE 2

2-[3-(1-Hydroxy-2,2-dimethylhexyl)phenoxy-methyl]quinoline

A. The ketone 2-(3-(2,2-dimethylhexanoyl)phenoxy-methyl)quinoline (4 g) was treated with sodium borohydride (0.9 g) in ethanol (70 ml) at room temperature for about 15 hours. The solution was cooled in an ice bath, and excess of borohydride was destroyed by adding cold, dil HCl solution dropwise. After all the reducing agent was destroyed, the pH of the solution was adjusted to about 5-6, and then most of the volatiles were removed. The residue was taken up in ethyl acetate, and the organics were washed with water, brine and dried over $MgSO_4$. The crude alcohol was isolated by removing all solvents. The pure alcohol (1.6 g, 114-116°C.), was isolated by chromatography on silica gel using 20% ethyl acetate in hexane as eluent.

B. Preparation of 2-(3-(2,2-dimethylhexanoyl)phenoxy-methyl quinoline (starting compound for A. procedure):

A mixture of 2-chloromethylquinoline (12.1 g), 3-(2,2-dimethylhexanoyl)phenol (15 g), finely powdered anhydrous potassium carbonate (20 g) and potassium iodide (0.05 g) in dry acetone (300 ml) was refluxed overnight. The suspension was filtered, and most of the volatiles were removed at the rotary evaporator. The residue was taken up in ethyl acetate, washed with 5% NaOH solution, water, brine, and the extract was dried. On removal of all solvent, the crude ether was obtained as a yellow oil. This oil was purified on HPLC (Prep. 500, Waters) using 10% ethyl acetate in hexane as eluent. The pure material was isolated in about 48% yield (12 g) as a light yellow oil.

-19 -

1 C. Synthesis of 3-(2,2-dimethyl hexanoyl)phenol

The benzyl ether of the desired phenol (26 g) was taken in methanol (150 ml) and this solution was hydrogenated in a Parr apparatus under an atmosphere of hydrogen (45-50 lbs./sq.in.) in the presence of 10% palladium on charcoal (10 g). After 20-24 hours, the suspension was filtered on celite, all methanol was removed to obtain the desired phenol in about 83% yield (15.4 g) as a colorless liquid.

10 The benzyl ether starting compound was prepared by oxidation of 3-(1-hydroxyhexyl)phenyl benzyl ether to the corresponding ketone followed by alkylation with methyl iodide to form the 2,2-dimethyl compound.

15 In similar manner, using appropriate starting materials and reagents, the following compounds and the corresponding ketones are prepared:

- 2-[3-(1-hydroxy-2-isobutylhexyl)phenoxyethyl]benzofuran;
2-[3-(1-hydroxy-2,2-diethylpentyl)phenoxyethyl]thiophene; and
20 2-[3-(1-hydroxy-2-methylhexyl)phenoxyethyl]benzothiophene.

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EXAMPLE 3

2-[3-(1-Hydroxyhexyl)phenoxy]methylpyridine hydrochloride

A suspension of 3.3 g of picolyl chloride hydrochloride (Aldrich 16,270-1), 1-(3-hydroxyphenyl)-1-hexanol (3.9 g), cesium carbonate (16.3 g), cesium iodide (trace) and acetone were refluxed for 40 hours. The reaction was filtered through a pad of celite and silica gel and the solvent removed in vacuo. The remaining oil was dissolved in ethyl ether, filtered through celite and silica gel and treated with ethereal hydrochloric acid. The resulting white precipitate was filtered, washed (ethyl ether) and dried giving 4.2 g (66% yield) of solid, m.p. 164-165°C.

In like manner as above using appropriate starting materials and reagents, the following compounds were prepared:

3-[[3-(1-Hydroxyhexyl)phenoxy]methyl]pyridine hydrochloride, m.p. 162-163°C;

2-[[3-(1-Hydroxyhexyl)phenoxy]methyl]quinoline hydrochloride, m.p. 90-95°C; and

4-[[3-(1-Hydroxyhexyl)phenoxy]methyl]pyridine hydrochloride, m.p. 160-160.5°C.

EXAMPLE 4

Methyl 6-[[3-(1-hydroxyhexyl)phenoxy]methyl]picolinate

A solution of 6-[[3-(1-hydroxyhexyl)phenoxy]-methyl]picolinylnitrile (1.1 g), methanol (50 ml) and cesium carbonate was stirred at room temperature overnight. The reaction mixture was diluted with 0.1N hydrochloric acid. After stirring for three hours, the methanol was removed in vacuo and the remaining suspension was extracted with chloroform. The organic extract was dried (MgSO_4) and concentrated to an oil (7.6 g, 94% yield).

In like manner as above, using appropriate starting materials and reagents, the following compounds were prepared:

Ethyl 2-(3-(2-quinolinylmethoxy)phenoxy)propionic acid;
Ethyl 2-(3-(2-quinolinylmethoxy)phenyl)propionic acid.

EXAMPLE 5

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2-(3-(2-(2-Hydroxy)heptyl)phenoxy)methyl)quinoline hydrochloride

A mixture of 2-chloromethyl quinoline hydrochloride (3.1 g) and 2-(3-hydroxyphenyl)-2-heptanol (3 g) in acetone (300 ml) containing potassium carbonate (20 g) and potassium iodide (0.2 g) was refluxed overnight. The reaction mixture was cooled, and most of the volatiles were removed at the rotary evaporator. The residue was taken up in ethyl acetate, and was washed with sodium hydroxide solution (5%) and brine. The organic layer was dried over magnesium sulfate and all solvent was removed to leave the crude product (weighing about 6 g), which was purified by chromatography (silica gel; 20% ethyl acetate in hexanes). The free base, isolated as an oil, was dissolved in dry ether, and treated with hydrogen chloride gas to give the pure desired salt as a white solid, m.p. 125°C. (dec.).

In like manner as described above, using appropriate starting materials and reagents, 2-(3-(2-(2-hydroxy)heptyl)phenoxy)methyl)pyridine hydrochloride, m.p. 160-165°C., was prepared.

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-23 -

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EXAMPLE 62-[3-(1-Hexenyl)phenoxy-methyl]quinoline

Sodium ethoxide was prepared by dissolving sodium metal (0.9 g) in absolute ethanol (50 ml).

5 3-Hydroxy-benzaldehyde (5 g) in alcohol (50 ml) was added to sodium ethoxide and the mixture was refluxed for one hour. The reaction mixture was cooled, and a solution of 2-chloromethyl quinoline (7.3 g) in alcohol (50 ml) was added. The mixture was refluxed for one day.

10 All volatiles were removed, and the residue was taken up in ethyl acetate. The organic extract was washed with aqueous sodium hydroxide (5%) solution, water and brine. After drying, all solvent was removed. The residual oil was chromatographed on silica gel using
15 15% ethyl acetate in hexane as eluent and the pure aldehyde was isolated.

N-pentyl-triphenylphosphonium bromide (3.1 g), prepared by refluxing a toluene solution of 1-bromopentane and triphenylphosphine, and filtering the white
20 phosphonium salt, was dissolved in tetrahydrofuran (100 ml.) The solution was cooled to 0°C., and n-butyl lithium (7.6 mmol; 2.3 M solution in hexane) was added. The mixture was stirred at room temperature for one hour, then cooled again to 0°C., and a solution of the above alde-
25 hyde (2 g) in tetrahydrofuran (35 ml) was added. The reaction mixture was stirred at room temperature overnight. Most tetrahydrofuran was removed, and the residue was taken up in ethyl acetate. The organic layer was washed with water, brine, and dried over magnesium
30 sulfate. All solvents were removed, and the crude product was purified on silica gel using 15% ethyl acetate in hexane as eluent. The desired compound was isolated as a light yellow liquid (0.8 g).

-24-

EXAMPLE 7

2-[3-(1-Hydroxyethyl)phenoxyethyl]quinoline

3 A mixture of 3-(1-hydroxyethyl)phenol
5 (7 g), 2-chloromethylquinoline (9 g), potassium
carbonate (7 g) and potassium iodide (0.3 g) in
acetone (75 ml) was refluxed overnight. The
reaction mixture was poured into water, and then
thoroughly extracted with ethyl acetate (3 x 30 ml).
The organic extract was washed with NaOH solution
10 (1 N), water, brine, and then dried over MgSO_4 .
All volatiles were removed to obtain a dark
brown liquid, which was chromatographed on silica
gel (12% ethyl acetate in hexanes) to leave the
desired product as a light yellow liquid.

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EXAMPLE 8

2-[3-(1-N-methylaminohexyl)phenoxyethyl]quinoline

A solution of 2-[3-(hexanoyl)phenoxyethyl]-
quinoline (2.8 g), 40% aqueous methylamine (1.5 ml)

5 and methanol adjusted to pH 6 with 5% aqueous hydrochloric
acid is treated with a methanolic solution of sodium
cyanoborohydride. The reaction is stirred overnight.

The methanol is removed in vacuo and the remaining
mixture is extracted with methylene chloride. The organic
10 extract is dried (MgSO_4) and concentrated to an oil.

In like manner as above, using appropriate
starting materials, the following compounds can be
prepared:

15 2-[3-(1-n-butylaminoethyl)phenoxyethyl]quinoline; and
2-[3-(1-N,N-dimethylaminoethyl)phenoxyethyl]pyridine.

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EXAMPLE 92-[3-(2-hydroxy-2-heptyl)phenoxyethyl]quinoline

To an ethereal solution of 2-(3-hexanoyl-
phenoxyethyl)quinoline (3.2 g) (prepared by oxidation
5 of the corresponding alcohol with pyridinium chloro-
chromate in CH₂Cl₂) is added slowly an excess of a 3M
solution of methylmagnesium bromide (2.5 g; 7.0 ml) in
ether and the mixture stirred overnight. A saturated
solution of ammonium chloride is added dropwise to the
10 well-stirred reaction mixture until the solution became
clear, and a gray-white solid coagulated to form a hard
cake. The liquid was filtered, and the residue was
washed with more ether. The ether layer was separated
from the aqueous layer, washed with brine, and dried over
15 magnesium sulfate. All volatiles were removed to give
an oil, which was purified by chromatography on silica
gel (6% ethyl acetate in hexane) to get the desired
tertiary alcohol as a clear, colorless liquid.

In the same manner, using appropriate starting
20 materials and reagents, the following compounds are
prepared:

2-[3-(2-hydroxy-2-heptyl)phenoxyethyl]pyridine; and
2-[3-(1-hydroxy-2,2-dimethylbutyl)phenoxyethyl]quinoline.

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EXAMPLE 103-(3-(1-Hydroxyhexyl)phenoxy)methylquinoline

To a solution of 3-chloromethylquinoline (10 g, 0.056 mol; prepared from 3-hydroxymethylquinoline and thionyl chloride) and 3-(1-hydroxyhexyl)phenol (12 g, 0.062 mol) in DMSO (200 ml) was added a 2N solution of sodium hydroxide (31 ml, 0.062 mol). The solution became warm (40-45°C.). This was allowed to stir at room temperature for 5 hours. The dark reaction mixture was poured into water, and the aqueous solution was thoroughly extracted (4 x 50 ml) with ethyl acetate. The organic extract was washed with 1N NaOH solution, water and then brine. After drying over anhydrous magnesium sulfate, all volatiles were removed. The dark residual liquid on trituration with ether-petroleum ether (1:2) yielded a beige colored solid, which on recrystallization from hexane-ethyl acetate gave the desired material (12.9 g, 69%) as an off-white solid.

In a similar manner, starting from 6-chloromethylquinoline and 3-(1-hydroxyhexyl)phenol, the other isomeric compound, 6-(3-(1-hydroxyhexyl)phenoxy)methylquinoline, can be prepared.

EXAMPLE 11

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2-(3-(2-Quinolinylmethoxy)phenoxy)propionic acid (hydrochloride salt)

Ethyl 2-(3-(2-quinolinylmethoxy)phenoxy)propionate
5 (3.6 g; m.p. 58-60°C.) was taken up in 10% hydrochloric acid solution (180 ml), and the mixture was heated at 100°C. for 26 hours. On cooling the reaction mixture in an ice bath, the desired carboxylic acid crystallized as a hydrochloride salt (3.6 g), which was recrystallized
10 from ethanol to give the desired acid, as its hydrochloride salt, as colorless crystals, (2.2 g; m.p. 184-185°C.).

In a similar manner, starting from ethyl 2-(3-(2-quinolinylmethoxy)phenoxy)propionate (2.5 g) and hydrochloric acid (90 ml, 4N), 2-(3-(2-quinolinylmethoxy)-
15 phenoxypropionic acid (hydrochloride salt; 1.3 g; m.p. 136-138°C.) can be prepared.

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-29 -

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EXAMPLE 12

2-(3-(1-Hydroxyhexyl)benzyloxymethyl)quinoline

5 A mixture of 2-hydroxymethylquinoline (8 g,
0.05 mol) and 3-(1-hydroxyhexyl)benzyl p-toluene-
sulfonate (18.2 g, 0.05 mol;
in methylene chloride (200 ml) containing triethylamine
(15 ml) was stirred at 0°C. for 4 hours, and then allowed
to warm up to room temperature. This mixture was
stirred for two more hours at this temperature, and then
10 poured into water. The organic layer was separated and
washed with dilute sodium hydroxide solution, water
and brine. After drying the organics, all volatiles
were removed to obtain the crude product as a yellowish
brown liquid. This was purified by chromatography
15 on silica gel using 15% ethyl acetate in hexanes to get
the pure product as a clear, light yellow liquid
(9 g, 52% yield).

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EXAMPLE 13

3-(2-Quinolinylmethoxy)phenylacetic acid

5 A mixture of 2-chloromethyl quinoline (2.3g, 13.3 mmol), 3-hydroxyphenyl acetate (2.2g, 13.3 mmol), excess powdered potassium carbonate (10g) and a catalytic amount of potassium iodide (0.1g) in dry acetone (150 ml) was refluxed overnight (18 hr.). The reaction mixture was filtered, and the filtrate was concentrated, taken up in ethyl acetate, and the organic extract was washed with
10 a 5% NaOH solution and brine. After drying over $MgSO_4$, all volatiles were removed from the organic extract, and the crude oil was chromatographed on silica gel (20% ethylacetate in hexanes) to obtain the methyl ester of the desired product (3.0g).

15 The above ester (3.0g) was dissolved in 4N HCl solution, and this was refluxed for 4 hours. On cooling in an ice bath, the product crystallized out as the hydrochloride salt. This salt was purified further by recrystallization twice from ethanol. The desired product
20 was obtained as the hydrochloride salt, as slightly pink crystals (2.5g), and slowly decomposes with melting above 180°C.

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-31-

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EXAMPLE 14

2-(3-(6-Phenoxy-1,2,2-trimethyl-1-hydroxyhexyl)phenoxy-
methyl) quinoline

To a solution of the ketone, 2-(3-(6-phenoxy-
5 2,2-dimethyl hexanoyl)phenoxy-methyl) quinoline (3.6g) in
dry ether (100 ml) at 0°C, was added dropwise, an ethereal
solution of methyl magnesiumbromide (7.7 ml, 23.8 mmol,
3 eqv.) under an atmosphere of nitrogen. The clear orange
solution was stirred overnight at room temperature. To
10 this solution, a saturated ammonium chloride solution was
added when the magnesium salts precipitated. The ether
layer was separated, washed with water and brine, and then
dried over MgSO_4 . All volatiles were removed to obtain the
crude product (4.2g). This was purified by chromato-
15 graphy on silica gel (25% ethyl acetate in hexanes, 20%
ethyl acetate in hexanes and finally 10% ethyl acetate in
hexanes) to obtain the pure product as a yellow liquid (0.9g).

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EXAMPLE 152-(3-Hexylphenoxy)methyl quinoline

A solution of 99% pure 2-(3-(1-hexenylphenoxy)methyl) quinoline (1.5g) in ethanol (20 ml) containing 10% Pd-C catalyst (0.5g) was exposed to an atmosphere of hydrogen at 10 psig for one hour. The catalyst was filtered through a bed of celite, and all ethanol was removed to obtain the pure desired saturated compound (1.1g) as a yellow liquid.

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EXAMPLE 161-(3-(2-Quinolinylmethoxy)phenyl)-3-methyl-1,3-butane diol

A mixture of 2-chloromethyl quinoline hydrochloride (10g, 47 mmol), 3-hydroxybenzaldehyde (6.3g, 52 mmol),
5 powdered potassium carbonate (14.5g, 105 mmol), catalytic amounts of cesium carbonate (1.5g) and sodium iodide (0.7g) in dry acetone (150 ml) was refluxed for 14 hours. The solid residue was filtered off, and the filtrate was concentrated and dissolved in ethyl acetate. The organic
10 solution was washed successively with 10% NaOH solution, water and brine and then dried over MgSO_4 . All volatiles were removed to leave a yellowish solid weighing 14.8g. This was recrystallized from hexanes-ethanol mixture to obtain 4-(3-(2-quinolinylmethoxy)phenyl-4-hydroxy-2-
15 butanone as off-white crystals (11.8g), mp 116-9°C.

To a solution of the above hydroxy-ketone (2.5g) in dry THF (150 ml) was added dropwise, an ethereal solution of methyl magnesium bromide (17.1 mmol, 2.2 eqv.). The reaction mixture was stirred overnight, and then a saturated
20 ammonium chloride solution was added. The precipitated magnesium salts were filtered, and the filtrate was concentrated in vacuo. The desired material was isolated after purification by chromatography on silica gel using 40% ethyl acetate in hexanes, as a yellowish crystalline
25 solid, mp 117-124°C (1.2g).

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EXAMPLE 17

2-(3-(6,6,6-Trifluorohexanoyl)phenoxy)methyl quinoline

A mixture of 3-(5,5,5-trifluorohexanoyl)phenol
(6.8g, 27 mmol) and 2-chloromethylquinoline (4.4g, 25 mmol)
5 in DMSO (75 ml) containing 2N NaOH solution (14 ml) was
stirred at room temperature overnight (13 hrs.). The
dark reaction mixture was poured into water (200 ml)
and the aqueous solution was extracted with ethyl acetate
(4 x 30 ml). The organic extract was washed with 1N NaOH
10 solution, water and brine and then dried over MgSO_4 .
After removal of all volatiles, a dark liquid was obtained
which solidified on standing (7.2g). This solid was
chromatographed (3% ethanol in toluene on silica gel) to
obtain a beige color solid (4.5g; mp 83-4°C), which was
15 chromatographed again (15% acetone in hexanes on silica
gel) to get a white solid (3.1g; mp 86-87°C). This pure
material was recrystallized from hexanes-acetone (trace)
to leave the desired compound as a colorless, crystalline
solid (2.4g), mp 88-88.5°C (first crop; second crop
20 mp 87-88°C).

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EXAMPLE 18

2-(3-(5,5,5-Trifluoropentanoyl)phenoxyethyl) quinoline

This material was synthesized by refluxing a mixture of 2-chloromethyl quinoline (2.6g, 14.5 mmol),
5 3-(5,5,5-trifluoropentanoyl)phenol (3.7g, 15.9 mmol), powdered potassium carbonate (6.0g, 43.5 mmol) and a catalytic amount of potassium iodide (0.1g) in dry acetone (50 ml) for 14 hours. After this period, the mixture was filtered, and the filtrate was concentrated.

10 The residue was dissolved in ether, and the ethereal solution was washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. The pure desired ketone was isolated by chromatography on silica gel using 20% ethyl acetate in hexanes as eluent. The product was obtained in
15 62% yield (3.4g), had a melting point 80-82°C and was a yellowish solid.

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EXAMPLE 19

2-(3-(6-Benzoyloxy-1-hydroxyhexyl)phenoxyethyl) quinoline

- 2-Chloromethyl quinoline (3.6g) was refluxed
with 3-(6-benzoyloxy-1-hydroxyhexyl)phenol (4.2g), powdered
5 potassium carbonate (8g) and potassium iodide (0.2g)
in dry acetone (150 ml) overnight (16 hrs.). The suspension
was filtered, the filtrate was concentrated in vacuo and
then taken up in ethyl acetate. This solution was washed
with 5% NaOH solution, water and brine and then dried.
10 All solvent was removed to obtain the crude product which
was purified by chromatography (silica gel; 30% ethyl
acetate in hexanes). The pure compound was dissolved in
ether, and was precipitated as the hydrochloride salt
with dry ethereal solution of HCl. The pure salt was
15 filtered, washed with cold water, and dried in vacuo to
yield a tan powder (1.5g), mp 86-89°C.

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EXAMPLE 20

Methyl 3-(3-(2-quinolinylmethoxy)benzoyl)propanoate

A mixture of pure methyl 4-(3-(2-quinolinylmethoxy) phenyl-4-hydroxy butyrate (1.1g) and activated
5 manganese dioxide (6.2g) in methylene chloride (25 ml) was stirred at room temperature. After 20 hours, no starting material was detected by thin layer chromatography. The manganese dioxide was filtered through celite, and the methylene chloride solution was concentrated in vacuo.

10 The residue was purified by chromatography on silica gel using 15% ethyl acetate in hexanes containing 1% acetic acid as eluent. The desired keto-ester was obtained (0.22g) as an off-white solid, mp 80-81°C.

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EXAMPLE 21Synthesis of 5-phenoxy-pentyl bromide

To a well-stirred suspension of sodium hydride (15.3g, 0.32 mol; 50% oil dispersion) in dry DMF (500 ml) containing (25g, 0.26 mol), was added dropwise 1,5-dibromopentane (122.2g, 0.53 mol). After the addition was complete, the reaction mixture was stirred at 60-70°C for 4 hours. Most of the DMF was next removed under reduced pressure, and the residue was dissolved in ethyl acetate (250 ml). The organic extract was washed successively with a 5% sodium hydroxide solution, water and brine. After drying the organics over anhydrous magnesium sulfate, all volatiles were removed. The residual yellow liquid was then distilled under reduced pressure, and the pure product was collected at 118-125°C/1 mm as a clear colorless liquid (26g, 40% yield).

Synthesis of 3-(6-phenoxy-1-hydroxyhexyl)phenol

To gently refluxing dry tetrahydrofuran (70 ml) containing magnesium turnings (1.1g, 44 mmol) and a small crystal of iodine, was added dropwise from a dropping funnel a solution of 5-phenoxy-pentyl bromide (11.0g, 45 mmol) in dry THF (50 ml). After about 5-7 minutes, the Grignard reaction started as indicated by the disappearance of the brown iodine color. The heating was adjusted so that the solution refluxed gently. After the addition of the halide was complete (ca. 30 min.), the clear solution was refluxed for about 1 hour. This solution of the Grignard reagent was cooled to room temperature.

A solution of 3-hydroxybenzaldehyde (5.0, 41 mmol) in dry THF (50 ml) was added dropwise to a well-stirred suspension of sodium hydride (2.5g, 52 mmol; 50% oil dispersion) in dry THF (50 ml) at room temperature. The

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-39 -

1 temperature was not allowed to go above ca. 40°C.
After the addition of 3-hydroxybenzaldehyde was complete
(ca. 30 min.) the slightly cloudy solution was warmed to
5 resulting clear solution of sodium 3-formyl phenoxide
was cooled to room temperature and added dropwise using a
cannula, to the well-stirred solution of the Grignard
reagent (whose preparation was described above). A thick
precipitate immediately formed. This mixture was main-
10 tained at 40-45°C during the addition of the sodium salt.
After the addition was complete (ca. 2 hours), the reaction
mixture was stirred at this temperature for another hour,
and then cooled in an ice bath. The excess reactive
materials (sodium hydride, Grignard reagent, etc.) were
15 destroyed slowly by carefully adding methanol (30 ml),
and then a saturated ammonium chloride solution (350 ml)
was added to dissolve all solids. The organic layer was
separated, and the aqueous layer was extracted with ether
(2 x 75 ml). The combined organics were washed with water,
20 brine, and then dried over anhydrous magnesium sulfate.
After drying the extract, all volatiles were removed to
obtain a dark liquid. This oil was titrated with a
1:1 mixture of ether and petroleum ether (35-55°C) when an
off-white solid was obtained (12g). This can be crystallized
25 from methanol-ethyl acetate to give a white solid, mp 148-9°C.
Synthesis of 2-[3-(6-phenoxy-1-hydroxyhexyl)phenoxymethyl]
quinoline

A mixture of 2-chloromethyl quinoline (1.1g;
6.3 mmol), 3-(6-phenoxy-1-hydroxyhexyl)phenol (1.8g,
30 6.3 mmol) and finely powdered anhydrous potassium carbonate
(1.74g, 12.6 mmol) in acetone (40 ml) containing catalytic
amounts of finely powdered, anhydrous cesium carbonate

-60-

0181568

1 (0.4, 1.3 mmol) and sodium iodide (0.05g, 0.33 mmol) was
refluxed overnight (15 hours). The reaction mixture was
cooled to the room temperature and filtered. The solid
residue was washed thoroughly with acetone (3 x 15 ml),
5 and all the filtrates were combined. All volatiles were
removed from the combined acetone filtrate to leave a
light yellow viscous liquid which solidified to an off-white
solid on tituration with a 1:1 mixture of ether and petroleum
ether (35-55°C). This solid was chromatographed on silica
10 gel with 35% ethylacetate in hexanes to yield the desired
product (1.6g, 60%) as a white crystalline solid, mp 83-84.5°C.

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EXAMPLE 22

2-[3-(1-Hydroxyhexyl)phenoxyethyl]-1,2,3,4-tetrahydro-
naphthalene

A mixture of 4.0 g (0.018 mol) 2-(iodomethyl)-
5 1,2,3,4-tetrahydronaphthalene, 3.4 g (0.018 mol) 3-(1-
hydroxyhexyl)phenol and 3.4 ml NaOH (5N) in 50 ml
DMSO and 20 ml THF was stirred at room temperature
for a period of 48 hours. The reaction mixture was
concentrated under reduced pressure. The concentrated
10 reaction mixture was poured into water and extracted
with ether. The ether extract was washed with water,
dried over MgSO_4 and concentrated to dryness under reduced
pressure. The residue was passed through a silica gel
column using hexane/ethyl acetate (3:1) as eluent.
15 Evaporation of eluent gave an oily product (1.3 g).

The product was evaluated for 5-lipoxygenase
pathway inhibition ($5\text{-LOX}/I_{50}/\mu\text{M}$) and a value of $6.0/\mu\text{M}$
obtained.

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EXAMPLE 232-(3-(1-Hydroxyhexyl)phenoxyethyl)naphthalene

A suspension of 2-bromomethyl naphthalene (5 g, 0.023 mol), 3-(1-hydroxyhexyl)phenol (5 g, 0.026 mol), powdered potassium carbonate (4.5 g, 0.033 mol), sodium iodide (0.4 g, 0.0023 mol) and cesium carbonate (0.7 g, 0.0021 mol) in dry acetone (75 ml) was refluxed overnight (14 hours). The reaction mixture was filtered, the filtrate was concentrated, dissolved in ether, and then washed successively with 1N NaOH solution 6N HCl solution, water and brine. After drying the organics over anhydrous MgSO_4 , all volatiles were removed. The crude product (5 g) was further purified by chromatography, using 8% ethylacetate in hexanes on silica gel, to yield 3.5 g of the pure desired compound as a colorless liquid.

The compound was evaluated for 5-lipoxygenase pathway inhibition ($5\text{-LOX}/I_{50}/\mu\text{M}$) and a value of $5.0 \mu\text{M}$ obtained.

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EXAMPLE 242-(3-Hexanoylphenoxy)methyl naphthalene

5 A mixture containing 2-bromomethyl naphthalene (3.0 g, 13.5 mmol), 3-hexanoylphenol (2.6 g, 13.5 mmol), powdered potassium carbonate (19.0 g, 135 mmol) and potassium iodide (0.1 g) in dry acetone (100 ml) was refluxed for two days. Most of the solvent was removed after filtering off the solid residue. The oil was purified by chromatography on silica gel using a 5% ethylacetate in
10 hexane solution as eluent to leave the desired product as a clear, colorless liquid (2.6 g).

When evaluated, the product showed some 5-lipoxygenase inhibition (5-LOX/ I_{50} μ M).

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-44-

1 The following protocol describes an assay to detect
inhibitors of the lipoxygenase pathway. Such inhibitors are
believed to be capable of modulating the biosynthesis of the
5 leukotrienes, a property believed to be useful in treating
asthma and inflammatory disease states.

10 Protocol for Detecting Inhibitors of the Lipoxygenase Pathway

 A suspension of rat neutrophils in buffer is incubated
for 3 minutes at 30°C with [¹⁴C]-arachidonic acid (AA) and
15 Calcium Ionophore A23187. Citric Acid (2M) is used to quench
the reaction. Following the addition of a trace amount of
(³H)-5-HETE together with an excess of unlabeled 5-HETE to
each tube, the mixture is extracted with chloroform/methanol.
20 The organic layer is washed with dilute acid and an aliquot is
transferred to glass tubes and dried. The residue is dissolved
in a small volume of chloroform and an aliquot is spotted on
silica gel TLC sheets, which are developed with an ethyl
25 acetate/isooctane/water/acetic acid solvent system. The 5-HETE
spots are visualized with iodine, cut out and placed in
scintillation vials for counting. After adjusting for the
extraction efficiency, the amount (pmole) of [¹⁴C]-5-HETE in
30 each of the tubes is quantitated. The net pmoles of 5-HETE are
obtained by subtracting the pmoles of 5-HETE in the tubes

1 containing buffer alone (blank) from the pmoles of 5-HETE in
the tubes containing buffer and cells (control). The ability
of the test compounds to modulate the activity of this enzyme
5 is determined by a decrease or increase in the net amount of
5-HETE produced.

Table I shows the concentration
required for 50% inhibition of the 5-lipoxygenase pathway
10 (5-LOX/ I_{50} μ M) for representative compounds according to the
present invention.

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TABLE I

$\text{Ar}_1 - \text{X} - \text{Ar} - \text{Z} - (\text{R})_n$

5-LOX
I₅₀ μM

Ar_1	X	Ar	Z(R) _n	5-LOX I ₅₀ μM
2-quinolyl	-CH ₂ O-	C ₆ H ₄ *	3-(CH(C ₅ H ₁₁) _{OH}) **	0.16
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(C(CH ₃)C ₅ H ₁₁) _{OH}	0.1
2-pyridyl	-CH ₂ O-	C ₆ H ₄	3-(-CH(C ₅ H ₁₁) _{NHCH₃})	2.2
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(-CH=CHC ₄ H ₉) **	2.4
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(CH(C ₅ H ₁₀ -O- ) _{OH})	0.6
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(CH-C ₅ H ₁₀ OC ₆ H ₅) _{OH}	0.6
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(C(CH ₃)C ₅ H ₁₀ -OC ₆ H ₅) _{OH}	0.8
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(CHCH(CH ₃)C ₄ H ₉) _{OH}	0.2
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(CHC(CH ₃) ₂ C ₄ H ₉) _{OH}	0.27
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(C(CH ₃)C(CH ₃) ₂ C ₄ H ₉) _{OH}	0.27

* C₆H₄ is phenylene

** C₄H₉ and C₅H₁₁ are linear alkyl groups

TABLE I - Cont'd.

Ar ₁	X	Ar	Z(R) _n '	5-LOX I ₅₀ uM
2-quinolyl	-O-	C ₆ H ₄	4-(CH-C ₅ H ₁₁) OH	0.35
4-pyridyl	-CH ₂ O-	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	3
2-pyridyl	-CH ₂ O-	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	0.5
3-pyridyl	-CH ₂ O-	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	3
6-(2-carboxy- pyridyl	-CH ₂ O-	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	1.9
6-(2-cyano- pyridyl	-CH ₂ O-	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	30
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(CC ₅ H ₁₁) O	0.15
2-pyridyl	-CH ₂ O-	C ₆ H ₄	3-(C(CH ₃)C ₅ H ₁₁) OH	0.3
2-quinolyl	-CH ₂ O-	C ₆ H ₄	3-(CHCH ₂ CCCH ₃) OH O	0.18
2-quinolyl	-CH ₂ O-	C ₆ H ₄	4-(CHC ₅ H ₁₁) OH	0.35

0181568

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TABLE I - Cont'd.

$Ar_1 - x - \lambda r - z - (R)_n$

Ar ₁	X	Ar	Ar ₁ - X - Ar - Z - (R) _n	Z(R) _n	5-LOX I ₅₀ μM
3-carboxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁)	OH	25
2-carboxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁)	OH	30
2-carboxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₄ H ₉)	OH	10
4-carboxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁)	OH	21
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁)	OH	1.2
2-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁)	OH	0.6
2-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₄ H ₉)	OH	3.0
4-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁)	OH	3.2

0181563

-49-

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TABLE I - Cont'd.

$Ar_1 - X - Ar - Z - (R)_n$

5-LOX
I₅₀ μM

Ar_1	X	Ar	Z(R) _n	5-LOX I ₅₀ μM
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	2-(CHC ₅ H ₁₁) OH	3.2
3-carboxymethylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	
3-carbomethoxymethylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	5.8
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OCOCH ₃	5.0
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OCH ₃	10
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OTHP***	23
2-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₄ H ₉) OTHP	10
2-hydroxymethylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₄ H ₉) OH	4

***THP is tetrahydro-2H-pyran-2-yl-

35 30 25 20 15 10 5 1

TABLE I - Cont'd.

$Ar_1 - X - Ar - Z - (R)_n$

5-LOX
 $I_{50, \mu M}$

Ar_1	X	Ar	Z(R) _n	5-LOX $I_{50, \mu M}$
3-formylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₄ H ₉) OH	4.0
3-cyanophenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	17
3-aminomethylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	
3-carbamylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	2.0
4-acetoxymethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	4.8
phenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	2.7
phenyl	OCH ₂	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	6.7
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-(C=CHC ₄ H ₉) CH ₃	5.0

-50-

-50-

0181568

TABLE I - Cont'd.

$Ar_1 - X - Ar - Z - (R)_n$

Ar_1	X	Ar	Z(R) _n	5-LOX I ₅₀ uM
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	4-(CH=CHC ₄ H ₉)	100
phenyl	CH ₂ O	C ₆ H ₄	3-(C-C ₅ H ₁₁) O	2.0
phenyl	CH ₂ O	C ₆ H ₄	3-[CC(CH ₃) ₂ C ₄ H ₉] O	7.5
phenyl	CH ₂ O	C ₆ H ₄	3-[CHC(CH ₃) ₂ C ₄ H ₉] OH	2.5
phenyl	CH ₂ O	C ₆ H ₄	3-[CHCH(CH ₃)C ₄ H ₉] OH	3.0
3-carbomethoxyphenyl	CH ₂ O	C ₆ H ₄	3-[CHC(CH ₃) ₂ C ₄ H ₉] OH	2.0
phenyl	CH ₂ O	C ₆ H ₄	3-[C(CH ₃)C ₅ H ₁₁] OH	1.0
phenyl	CH ₂ O	C ₆ H ₄	3-[C(CH ₃)C(CH ₃) ₂ C ₄ H ₉] OH	2.4

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TABLE I - Cont'd.

$Ar_1 - X - Ar - Z - (R)_n$

5-LOX
I₅₀ μM

Ar_1	X	Ar	Z(R) _n	5-LOX I ₅₀ μM
phenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) N(CH ₃) ₃	22
phenyl	trans CH=CH	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	4.5
3-carbamylphenyl	CH ₂ O	C ₆ H ₄	3-(CC ₅ H ₁₁) O	0.7
3-cyanophenyl	CH ₂ O	C ₆ H ₄	3-(CC ₅ H ₁₁) O	8.0
phenyl	-O-	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	1.2
3-trifluoromethylphenyl	CH ₂ O	C ₆ H ₄	3-(CHC ₅ H ₁₁) OH	3.0

-52-
-52-

0181568

- 1 Using the procedures of the foregoing examples,
the following compounds are prepared:
- 2-[3-(1-hydroxyhexyl)phenoxymethyl]quinoline;
2-[3-(1-methyl-1-hydroxyhexyl)phenoxymethyl]quinoline;
- 5 2-[3-(1,2-dihydroxyhexyl)phenoxymethyl]quinoline;
2-[3-(2,2-dimethyl-1-hydroxyhexyl)phenoxymethyl]pyridine;
2-[3-(1,2,2-trimethyl-1-hydroxyhexyl)phenoxymethyl]quinoline;
2-[3-(1-methyl-1-hydroxyhexyl)phenoxymethyl]pyridine;
2-[3-(6-[3-chlorophenoxy]-1-hydroxyhexyl)phenoxymethyl]quinoline;
- 10 2-[3-(6-phenoxy-1-hydroxyhexyl)phenoxymethyl]quinoline;
2-[3-(6-phenoxy-2,2-dimethyl-1-hydroxyhexyl)phenoxymethyl]-
quinoline
2-[3-(6-[3-trifluoromethylphenoxy]-1-hydroxyhexyl)phenoxy-
methyl]quinoline;
- 15 2-[3-(1-hydroxyhexyl)phenoxymethyl]benzofuran;
2-[5-(1-hydroxyhexyl)-2-furyloxy)methyl]pyridine;
4-[5-(1-hydroxyhexyl)-2-thienylmethoxy]quinoline;
2-[6-(1-hydroxyhexyl)-3-pyridyloxy]quinoline;
3-[3-(1-hydroxyhexyl)phenoxymethyl]pyridine;
- 20 2-[3-(1-hydroxyethyl)benzylthio]pyridine; and
2-[3-(6-[3-chlorophenoxy]-1-methyl-1-hydroxyhexyl)phenoxy-
methyl]quinoline;
2-(3-(1-hydroxy-2,2-dimethyl-5,5,5-trifluoropentyl)-
phenoxymethyl)quinoline;
- 25 2-(3-(1,2,2,-trimethyl-5,5,5-trifluoro-1-hydroxy-
pentyl)phenoxymethyl)quinoline;
2-(3-(2,2-dimethyl-6,6,6-trifluoro-1-hydroxyhexyl)-
phenoxymethyl)quinoline;
- 30 2-(3-(1,2,2-trimethyl-6,6,6-trifluoro-1-hydroxyhexyl)-
phenoxymethyl)quinoline;

- 1 2-(3-(2,2-dimethyl-6,6,6-trifluoro-1-hydroxyhexyl)-
phenoxymethyl)pyridine;
3-(3-(2,2-dimethyl-6,6,6-trifluoro-1-hydroxyhexyl)-
phenoxymethyl)pyridine;
- 5 4-(3-(2,2-dimethyl-6,6,6-trifluoro-1-hydroxyhexyl)-
phenoxymethyl)quinoline;
2-(3-(6-methoxyhexyl)phenoxymethyl)quinoline;
2-(3-(4-methoxybutyl)phenoxymethyl)quinoline;
2-(4-(4-methoxybutyl)phenoxymethyl)quinoline;
- 10 2-(3-(6-phenoxyhexyl)phenoxymethyl)quinoline;
2-(3-(4-methoxybutyl)phenoxy)quinoline;
2-(3-(1,1,1-trimethylacetoxyl)phenoxymethyl)-
quinoline;
2-(3-(1-acetoxy-5,5,5-trifluoropentyl)-phenoxymethyl)-
15 quinoline;
2-(3-(1,1,1-trimethylacetoxyl-5,5,5-trifluoropentyl)-
phenoxymethyl)quinoline;
2-(3-(1,1,1-trimethylacetoxyl-6,6,6-trifluorohexyl)-
phenoxymethyl)quinoline;
- 20 2-(3-(2,2-dimethyl-1,1,1-trimethylacetoxyl)phenoxy-
methyl)quinoline;
2-(3-(2,2-dimethyl-6,6,6-trifluoro-1,1,1-trimethyl-
acetoxyl)phenoxymethyl)quinoline.
3-(3-(2-quinolinylmethoxy)benzoyl)propanoic acid;
- 25 5-(3-(2-quinolinylmethoxy)benzoyl)pentanoic acid;
methyl 5-(3-(2-quinolinylmethoxy)benzoyl)pentanoate;
methyl 4-(3-(2-quinolinylmethoxy)phenyl)-4-hydroxy butyrate;
4-(3-(2-quinolinylmethoxy)phenyl)-4-hydroxy butyric acid
(and the corresponding lactone);
- 30 methyl 6-(3-(2-quinolinylmethoxy)phenyl)-6-hydroxy hexanoate;
6-(3-(2-quinolinylmethoxy)phenyl)-6-hydroxy hexanoic acid
(and the corresponding lactone);

- 1 5-(3-(2-quinolinylmethoxy)phenyl)-5-hydroxy pentanoic acid
(and the corresponding lactone);
methyl 5-(3-(2-quinolinylmethoxy)phenyl)-5-hydroxy pentanoate;
methyl 4-(3-(2-quinolinylmethoxy)benzoyl)butyrate;
- 5 4-(3-(2-quinolinylmethoxy)benzoyl)butyric acid;
6-(3-(1-hydroxyhexyl)phenoxyethyl)-1,4-benzodioxan;
2-(3-(1-hydroxyhexyl)phenoxyethyl)-1,4-benzodioxan;
2-(3-(1-hydroxyhexyl)phenoxyethyl)quinoxaline
2-(3-(1-hydroxyhexyl)phenoxyethyl)-3-methyl quinoxaline;
- 10 7-(3-(1-hydroxyhexyl)phenoxyethyl)-5-methyl-1,8-
naphthyridin-2-ol;
2-(3-(1-hydroxy-6-phenoxyhexyl)phenoxyethyl)quinoxaline;
2-(3-(1-hydroxy-6-phenoxyhexyl)phenoxyethyl)-1,5-
naphthyridine;
- 15 2-(3-(1-hydroxy-6-phenoxyhexyl)phenoxyethyl)-1,6-
naphthyridine;
2-(3-(1-hydroxyhexyl)phenoxyethyl)pyrido(2,3-b)pyrazine;
2-(3-(1-hydroxy-6-phenoxyhexyl)phenoxyethyl)pyrido(3,4-b)
pyrazine;
- 20 2-(3-(1-hydroxyhexyl)phenoxyethyl)pyrido(3,4-d)pyrimidine;
2-(3-(1-hydroxy-6-phenoxyhexyl)phenoxyethyl)pyrido(4,3-d)
pyrimidine;
3-(3-(1-hydroxyhexyl)phenoxyethyl)piperazine-2,5-dione; and
3-(3-(6-phenoxy-1-hydroxyhexyl)phenoxyethyl)-2,5-dimethoxy-
- 25 3,6-dihydropyrazine.

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- 1 1-(3-phenoxyphenyl)-1-hexanol;
3-(1-hydroxyhexyl)phenyl-3-trifluoromethylbenzyl ether;
2-(3-(1-hydroxyhexyl)phenoxy methyl naphthalene;
3-(3-hexanoylphenoxy) methyl benzamide;
5 3-(3-hexanoyl phenxoy) methyl benzonitrile;
benzyl-3-(1-hydroxy-2-methyl hexyl)phenyl ether;
2-[2-(1-hydroxy hexyl)-5-pyridyloxy]benzene;
2-[2-(2-hydroxy hexyl)-3-pyranyloxy]benzene;
2-[2-(2-hydroxy heptyl)-4-thiopyranyloxy] benzene;
10 2-[2-(2-hydroxy heptyl)-5-quinolyloxy]benzene;
2-(3-(1-hydroxy-6,6,6-trifluorohexyl)phenoxy-
methyl)-1,4-naphthaquinone;
1-(3-(1-hydroxy-1-methylhexyl)phenoxymethyl)-2-
methoxy naphthalene;
15 1-(3-(6-phenoxy-1-hydroxyhexyl)phenoxymethyl)-4-
methoxy naphthalene;
2-(1-(3-(1-hydroxy-2,2-dimethylhexyl)phenoxy)
ethyl)naphthalene;
9-(3-(1-hydroxyhexyl)phenoxymethyl)anthracene;
20 9-(3-(1-hydroxyhexyl)phenoxymethyl)phenanthrene;
Methyl-3-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoate;
Methyl-2-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoate;
Methyl-4-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoate;
25 Methyl-3-[[2-(1-hydroxyhexyl)phenoxy]methyl]benzoate;
Methyl-3-[[3-(1-hydroxyhexyl)phenoxy]methyl]phenylacetate;
3-[[3-(1-Hydroxyhexyl)phenoxy]methyl]benzonitrile;
Methyl-2-[4-[[3-1-hydroxyhexyl)phenoxy]methyl]phenoxy]acetate;
30 Benzyl-3-[1-(hydroxy)hexyl]phenyl ether;
Methyl-3-[[3-1-methyl-1-hexenyl)phenoxy]methyl benzoate;
Methyl-3-[[4-(1-hexenyl)phenoxy]methyl benzoate;
Phenyl-3-cyanobenzyl ether;
35 3-(1-Hydroxyhexyl)phenyl-3-trifluoromethylbenzyl ether;
2-(3-(1-Hydroxyhexyl)phenoxy methyl naphthalene;

- 1 2-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoic acid;
3-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoic acid;
5-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoic acid;
4-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoic acid;
5 3-[[3-(1-hydroxyhexyl)phenoxy]methyl]phenyl
acetic acid;
methyl-3-[[3-(1-acetoxyhexyl)phenoxy]methyl]benzoate;
methyl-3-[[3-(1-methoxyhexyl)phenoxy]methyl]benzoate;
methyl-3-[[3-[1-(tetrahydro-2H-pyran-2-yloxy)-
10 hexyl]phenoxy] methyl]benzoate;
methyl-2-[[3-[1-(tetrahydro-2H-pyran-2-yloxy)-
pentyl] phenoxy]methyl]benzoate;
2-[3-(1-hydroxypentyl)phenoxy]methyl]benzenemethanol;
3-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzaldehyde;
15 phenyl-3-formylbenzyl ether;
3-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzyl amine
hydrochloride;
3-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzamide;
3-[3-hexanoyl phenoxy]methyl benzamide;
20 benzyl-3-(hexanoyl)phenyl ether;
3-[3-hexanoyl phenoxy]methyl benzonitrile;
benzyl-3-[1-(N-methylamino)hexyl]phenyl ether;
3-chlorobenzyl-3-[1-(n-butylamino)hexyl]phenyl
ether;
25 2-trifluoromethyl-3-[1-(N,N-dimethylamino)hexyl]-
phenyl ether;
benzyl-3-[1-hydroxy-2,2-(dimethyl)hexyl]phenyl ether;
2,4-dibromobenzyl-3-[1-(hydroxy)2-(isobutyl)hexyl]
phenyl ether;
30 4-fluorobenzyl-3-[1-(hydroxy)2-(diethyl)heptyl]-
phenyl ether;
benzyl 3-(1-hydroxy-2-methyl hexyl) phenyl ether;
3-(1-hydroxyhexyl)benzyl alcohol;
tolyl-3-(1-hydroxyhexyl)genzyl sulfonate;
35 methyl-3-[[3-(1-hydroxyhexyl)aniliny]methyl]benzoate;

- 1 ethyl-2-[[3-(1-hydroxybutyl)aniliny]methyl]benzoate;
isopropyl-4-[[3-(1-hydroxybutyl)aniliny]methyl]-
benzoate;
methyl-3-[[2-(1-hydroxyhexyl)aniliny]methyl]benzoate;
- 5 phenyl-3-[1-(hydroxyhexyl)benzyl thioether;
3-methoxyphenyl-3-[1-(hydroxy)hexyl]benzyl thioether;
4-nitrophenyl-3-[1-(hydroxy)hexyl]benzyl thioether;
methyl-2-[[3-(1-hydroxyhexyl)thiophenoxy]methyl]-
benzoate;
- 10 methyl 3-[3-(1-hydroxyhexyl) phenyl]amino]carbonyl]
benzoate;
2-(3-(1-hydroxy-6,6,6-trifluorohexyl)phenoxy)methyl)-
1,4-naphthaquinone;
1-(3-(1-hydroxy-1-methylhexyl)phenoxy)methyl)-2-
- 15 methoxy naphthalene;
1-(3-(6-phenoxy-1-hydroxyhexyl)phenoxy)methyl)-4-
methoxy naphthalene
2-(1-(3-(1-hydroxy-2,2-dimethylhexyl)phenoxy)-
ethyl) naphthalene;
- 20 9-(3-(1-hydroxyhexyl)phenoxy)methyl)anthracene;
9-(3-(1-hydroxyhexyl)phenoxy)methyl)phenanthrene;
3-(3-(1-hydroxyethyl)phenoxy)methyl benzoic acid;
3-(2-phenylethyl) hexanophenone;
methyl 3-(3-(1-hydroxyethyl)phenoxy)methyl benzoate;
- 25 3-hexanoyl diphenyl acetylene;
cis-3-(1-hydroxyhexyl) stilbene;
1-(3-(2-phenylethyl)phenyl-1-hexanol;
3-(1-hydroxyhexyl)diphenylacetylene;
trans-3-(1-hydroxyhexyl) stilbene;
- 30 trans-3-hexanoyl stilbene;
methyl 3-[3-[1-hydroxy-2,2-dimethylhexyl]phenoxy]-
methyl]benzoate;
cis-3-hexanoyl stilbene;
- 35

- 1 2-(3-hexanoylphenoxy) methyl naphthalene;
methyl 3-[3-(1-hydroxyhexyl) phenyl]amino]-
carbonyl] benzoate;
3-(2-quinolinylmethoxy)acetophenone;
5 2-(3-(1-hydroxy-5,5,5-trifluoropentyl)phenoxy-methyl)-
quinoline;
2-[3-(6-phenoxy-1-hydroxy-1-methylhexyl)phenoxy-
methyl]quinoline;
2-[3-(6-(3-chlorophenoxy)-1-hydroxy-1-methylhexyl)-
10 phenoxy-methyl]quinoline;
2-[3-(6-(3-trifluoromethylphenoxy)-1-hydroxy-1-
methylhexyl)phenoxy-methyl]quinoline;
3-[6-phenoxy-1-hydroxyhexyl]phenol;
3-[6-(3-trifluoromethylphenoxy)-1-hydroxyhexyl]phenol;
15 3-[6-(3-chlorophenoxy)-1-hydroxyhexyl]phenol;
2-[3-(6-(3-chlorophenoxy)-1-hydroxyhexyl)phenoxy-
methyl]quinoline;
2-[3-(6-phenoxy)-3-1-hydroxyhexyl)phenoxy-methyl]-
quinoline;
20 2-[3-(6-(3-trifluoromethylphenoxy)-1-hydroxyhexyl)-
phenoxy-methyl]quinoline;
2-[3-(1-acetoxyhexyl)phenoxy-methyl]quinoline;
2-[3-(1-methoxyhexyl)phenoxy-methyl]quinoline;
1-(2-thienyl)-2-(3-hexanoylphenyl) acetylene;
25 1-(2-thienyl)-2-[3-(1-hydroxyhexyl)phenyl]acetylene;
1-(2-quinolyl)-2-[3-(1-hydroxyhexyl)phenyl]acetylene;
1-(2-indolyl)-2-[3-(1-hydroxyhexyl)phenyl]acetylene;
1-(2-furyl)-2-[3-(1-hydroxyhexyl)phenyl]acetylene;
1-(2-thienyl)-2-[3-(1-hydroxyhexyl)phenyl]ethylene;
30 1-(2-quinolyl)-2-[3-(1-hydroxyhexyl)phenyl]ethylene;
1-(2-indolyl)-2-[3-(1-hydroxyhexyl)phenyl]ethylene;
1-(2-furyl)-2-[3-(1-hydroxyhexyl)phenyl]ethylene;

- 1 1-(2-thienyl)-2-(3-hexanoylphenyl)ethylene;
N-[3-(1-hydroxyhexyl)phenyl]pyridine-2-carboxamide;
2-[3-(1-hydroxyhexylbenzylamino)pyridine;
2-[3-(1-hydroxybutyl)anilinylmethyl]thiophene;
5 4-[3-(1-hydroxybutyl)anilinylmethyl]quinoline;
2-[2-(1-hydroxyhexyl)anilinylmethyl]quinoline;
3-methoxyphenyl-3-[1-(hydroxy)hexyl]benzyl thioether;
4-nitrophenyl-3-[1-(hydroxy)hexyl]benzyl thioether;
methyl-2-[[3-(1-hydroxyhexyl)thiophenoxy]methyl]-
10 benzoate;
2-(3-hexanoylphenoxymethyl)quinoline;
2-[2-(1-hydroxyhexyl)-5-pyridyloxy]quinoline;
4-[2-(1-hydroxyhexyl)-5-thienylmethoxy]quinoline;
2-[5-(1-hydroxyhexyl)-2-furylmethoxy]pyridine;
15 2-[5-(1-hydroxyhexyl)-2-pyridyloxymethyl]indole;
2-[4-(1-hydroxyhexyl)phenoxymethyl]pyrrole;

20

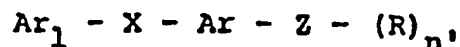
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1 WHAT IS CLAIMED IS

1. A compound of the formula:

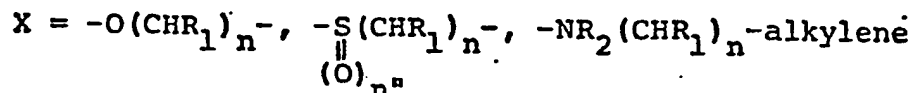


and the pharmaceutically acceptable salts thereof,
wherein

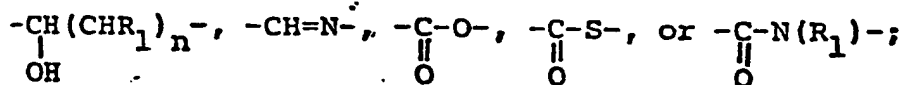
Ar_1 is a nitrogen, sulfur or oxygen heterocyclic ring or an aromatic ring;

Ar is a phenyl ring or a nitrogen, oxygen or sulfur heterocyclic ring;

Ar and Ar_1 may be fully substituted or less than fully substituted with H, CH_3 , lower alkyl, aryl, aralkyl, halo, hydroxy, lower alkoxy, CF_3 , carboxy, alkylcarboxy, arylcarboxy, alkylcarbalkoxy, alkanoyl, formyl, oxo, nitrilo, amino, aminoalkyl, alkylamine, carboxamide, aryloxy, nitro, sulfonyl, sulfonamide, thio, alkylthio, hydroxyalkyl or oxyalkylcarboxy;



of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms, $-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{CHR}_1)_n-$, $-\text{CH}(\text{CHR}_1)_n-$, $-\text{CH}=\text{N}-$, $-\text{C}(=\text{O})-\text{O}-$, $-\text{C}(=\text{O})-\text{S}-$, or $-\text{C}(=\text{O})-\text{N}(\text{R}_1)-$;

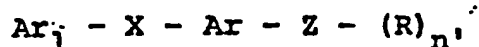


1 when $n'=1$, R is a substituent attached to one
 of the carbon atoms of Z selected from the group consisting
 of $=O$, OR_3 , SR_3 , $N(R_2)_2$, R_1 , and $-COR_4$ and when $n'=2$ one
 R is as previously defined, and the additional R is a substituent
 5 attached to one of the carbon atoms of Z selected from the
 group consisting of $=O$, OR_3 , SR_3 , $N(R_2)_2$, $-COR_4$, lactone
 and halo;

R_1 is H or CH_3 ;
 R_2 is H, lower alkyl, aryl or aralkyl;
 10 R_3 is H, lower alkyl, lower alkanoyl, aryl,
 aralkyl or substituted aryl in which the substituent is
 halo, lower alkyl or lower alkoxy;

R_4 is OR_2 or $N(R_2)_2$;
 $n = 0$ or 1 ;
 $n' = 1$ to 7 ; and
 15 $n'' = 0, 1$ or 2 .

2. A compound of claim 1 of the formula:



20 and salts thereof,

wherein

Ar_1 is quinolyl;

Ar is a phenyl, pyridyl or quinolyl ring;

25 $X = -O(CHR_1)_n-$, $-S(CHR_1)_n-$, $NR_2(CHR_1)_n-$, alkylene
 $(O)_n$

of up to 2 carbon atoms in the principal chain and up to
 a total of 4 carbon atoms, $-C(R_1)=C(R_1)-$, $-C\equiv C-$, $-\overset{\overset{O}{\parallel}}{C}(CHR_1)_n-$,

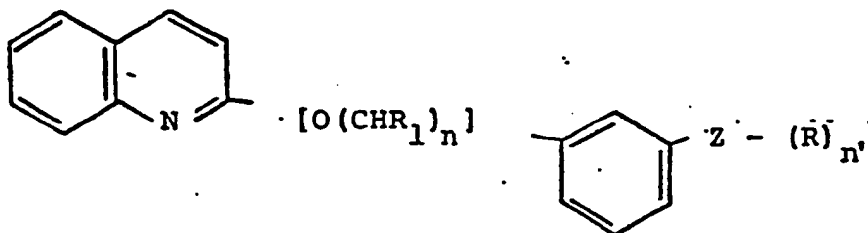
30 $-\underset{\underset{OH}{|}}{CH}(CHR_1)_n-$, $-CH=N-$, $-\overset{\overset{O}{\parallel}}{C}-O-$, $-\overset{\overset{O}{\parallel}}{C}-S-$, $-\overset{\overset{O}{\parallel}}{C}-N(R_1)-$;

- 1 Z is an alkylene chain containing up to 10
carbon atoms in the principal chain and a total of
up to 12 carbon atoms and from 0 to 2 double bonds;
each R is a substituent, attached to one of
5 the carbon atoms of Z selected from the group consisting
of =O, OR₃, SR₃, N(R₂)₂ and -COR₄;
R₁ is H or CH₃;
R₂ is H, lower alkyl, aryl or aralkyl;
R₃ is H, lower alkyl, lower alkanoyl, aryl or
10 aralkyl;
R₄ is OR₂ or N(R₂)₂;
n = 0 or 1;
n' = 1 to 7; and
n'' = 0, 1 or 2.

15

3. A compound of claim 1 of the formula:

20



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and salts thereof,
wherein

30

Z is an alkylene chain containing up to 10
carbon atoms in the principal chain and a total of up
to 12 carbon atoms and from 0 to 2 double bonds;

35

- 1 $n = 0$ or 1 ;
 $n' = 1$ to 7 ; and
 Each R is a substituent, attached to one of
 the carbon atoms of Z selected from the group consisting
 5 of $=O$, OR_3 , SR_3 , $N(R_2)_2$ and $-COR_4$;
 R_1 is H or CH_3 ;
 R_2 is H, lower alkyl, aryl or aralkyl;
 R_3 is H, lower alkyl, lower alkanoyl, aryl or
 aralkyl;
 10 R_4 is OH, OR_2 or $N(R_2)_2$;
 $n = 0$ or 1 ;
 $n' = 1$ to 7 ;
 with the proviso that one R is on the carbon
 atom of Z attached to the phenyl group.

- 15 4. The compound according to Claim 1 which
 is 2-[3-(1-methyl-1-hydroxyhexyl)phenoxy-methyl]quinoline,
 2-[3-(2,2-dimethyl-1-hydroxyhexyl)phenoxy-methyl]pyridine,
 2-[3-(1,2,2-trimethyl-1-hydroxyhexyl)phenoxy-methyl]quinoline,
 2-[3-(1-methyl-1-hydroxyhexyl)phenoxy-methyl]pyridine,
 20 2-[3-(6-(6-[3-chlorophenoxy]-1-hydroxyhexyl)phenoxy-
 methyl]quinoline or 2-[3-(6-phenoxy-1-hydroxyhexyl)-
 phenoxy-methyl]quinoline.

5. The compound according to Claim 1 which
 is 2-[3-(6-phenoxy-2,2-dimethyl-1-hydroxyhexyl)phenoxy-
 25 methyl]quinoline, 2-[3-(6-[3-trifluoromethylphenoxy]-1-
 hydroxyhexyl)phenoxy-methyl]quinoline, 2-[6-(1-hydroxy-
 hexyl)-3-pyridyloxy]quinoline, 2-[3-(6-[3-chlorophenoxy]-
 1-methyl-1-hydroxyhexyl)phenoxy-methyl]quinoline,
 2-(3-(1-hydroxy-5,5,5-trifluoropentyl)phenoxy-methyl)-
 30 quinoline or 2-(3-(1-hydroxy-5,5,5-trifluoropentyl)-
 phenoxy-methyl)pyridine.

1 6. The compound according to Claim 1 which
is 2-(3-(1-hydroxy-6,6,6-trifluorohexyl)phenoxyethyl)-
quinoline, 2-(3-(1-hydroxy-6,6,6-trifluorohexyl)phenoxy-
methyl)pyridine, 2-(3-(1-hydroxyheptyl)phenoxyethyl)-
5 quinoline, 2-(3-(1-hydroxyheptyl)phenoxyethyl)pyridine,
4-(3-(1-hydroxy-5,5,5-trifluoropentyl)phenoxyethyl)-
quinoline, 4-(3-(6-phenoxy-1-hydroxyhexyl)phenoxyethyl)
quinoline or 2-(3-(6-phenoxy-1-hydroxyhexyl)phenoxyethyl)
pyridine.

10 7. The compound according to Claim 1 which
is 2-(3-(1-hydroxy-1-methyl-5,5,5-trifluoropentyl)-
phenoxyethyl)quinoline, 2-(3-(1-hydroxy-2,2-dimethyl-
5,5,5-trifluoropentyl)-phenoxyethyl)quinoline,
2-(3-(1,2,2-trimethyl-5,5,5-trifluoro-1-hydroxypentyl)-
15 phenoxyethyl)quinoline, 2-(3-(1-methyl-1-hydroxy-5,5,5-
trifluoropentyl)-phenoxyethyl)quinoline, 2-(3-(2,2-
dimethyl-6,6,6-trifluoro-1-hydroxyhexyl)phenoxyethyl)-
quinoline, 2-(3-(1,2,2-trimethyl-6,6,6-trifluoro-1-hydroxy-
hexyl)phenoxyethyl)quinoline, 2-(3-(2,2-dimethyl-6,6,6-
20 trifluoro-1-hydroxyhexyl)-phenoxyethyl)pyridine,
3-(3-(2,2-dimethyl-6,6,6-trifluoro-1-hydroxyhexyl)-
phenoxyethyl)pyridine, 4-(3-(2,2-dimethyl-1-hydroxy-
hexyl)phenoxyethyl)quinoline or 2-(3-(6-methoxyhexyl)-
phenoxyethyl)quinoline.

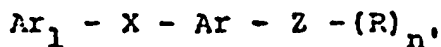
25 8. The compound according to Claim 1 which
is 2-(3-(4-methoxybutyl)phenoxyethyl)quinoline, 2-(4-
(4-methoxybutyl)phenoxyethyl)quinoline, 2-(3-(6-phenoxy-
hexyl)phenoxyethyl)quinoline, 2-(3-(4-methoxybutyl)-
phenoxy)quinoline, 2-(3-(1-acetoxyhexyl)phenoxyethyl)-
30 quinoline, 2-(3-(1-(1,1,1-trimethylacetoxy)hexyl)phenoxy-
methyl)quinoline, 2-(3-(1-acetoxy-5,5,5-trifluoropentyl)-
phenoxyethyl)quinoline, 2-(3-(1-(1,1,1-(trimethylacetoxy)-
5,5,5-trifluoropentyl)phenoxyethyl)quinoline,

- 1 2-(3-1-(1,1,1-(trimethylacetoxy)-6,6,6-trifluorohexyl)-
phenoxy)methyl)quinoline, 2-(3-(2,2-dimethyl-1-(1,1,1-
trimethylacetoxy)hexylphenoxy)methyl)quinoline, 2-(3-(2,
2-dimethyl-6,6,6-trifluoro-1-(1,1,1-trimethylacetoxy)-
5 hexyl)phenoxy)methyl)quinoline or ethyl 2-(3-(2-quinolinyl-
methoxy)phenoxy)propionate.

9. The compound according to Claim 1 which
is 2-(3-(2-quinolinylmethoxy)phenoxy)propionic acid,
ethyl 2-(3-(2-quinolinylmethoxy)phenyl)propionate,
10 2-(3-(2-quinolinylmethoxy)phenyl)propionic acid,
3-(3-(1-hydroxyhexyl)phenoxy)methyl)quinoline, 6-(3-
(1-hydroxyhexyl)phenoxy)methyl)quinoline, 2-(3-(1-
hydroxyhexyl)benzyloxymethyl)quinoline, 2-[3-(6(3-chloro-
phenoxy)-1-hydroxyhexyl)phenoxy)methyl]quinoline, 2-[(3-(6-
15 phenoxy)-1-hydroxyhexyl)phenoxy)methyl]quinoline,
2-(3-(6(3-trifluoromethylphenoxy)-1-hydroxyhexyl)-phenoxy-
methyl]quinoline, 3-[6-(3-chlorophenoxy)-1-hydroxyhexyl]-
phenol, 3-[6-phenoxy-1-hydroxyhexyl]phenol, 3-[6-(3-
trifluoromethylphenoxy)-1-hydroxyhexyl]phenol, 2-[3-
20 (6-phenoxy-1-hydroxy-1-methylhexyl)phenoxy)methyl]-
quinoline or 2-[3-(6-(3-chlorophenoxy)-1-hydroxy-1-
methylhexyl)phenoxy)methyl]quinoline.

10. The compound according to Claim 1 which
is 2-[3-(6-(3-trifluoromethylphenoxy)-1-hydroxy-1-methyl-
25 hexyl)phenoxy)methyl]quinoline, 3-(2-quinolinylmethoxy)
acetophenone, 2-[3-(1-Hydroxyhexyl)phenoxy)methyl]quinoline,
(2-quinolinylmethoxy)phenylacetic acid, 2-(3-(6-phenoxy-
1,2,2-trimethyl-1-hydroxyhexyl)phenoxy)methyl)quinoline,
2-(3-hexylphenoxy)methyl quinoline, 1-(3-(2-quinolinyl-
30 methoxy)phenyl)-3-methyl-1,3-butane diol, 2-(3-(6,6,6-
trifluorohexanoyl)phenoxy)methyl)quinoline, 2-(3-(5,5,5-
trifluoropentanoyl)phenoxy)methyl)quinoline, 2-(3-(6-
benzyloxy-1-hydroxyhexyl)phenoxy)methyl)quinoline, methyl(3-
(3-(2-quinolinylmethoxy)benzoyl)propionate or 2-[3-(6-
35 phenoxy-1-hydroxyhexyl)phenoxy)methyl]quinoline.

11. A compound of Claim 1 of the formula:



and salts thereof,

wherein

Ar_1 is a phenyl or naphthyl group;

Ar is a phenyl, pyridyl or quinolyl group;

$\text{X} = -\text{O}(\text{CHR}_1)_n-, -\text{S}(\text{CHR}_1)_n-, \text{NR}_2(\text{CHR}_1)_n-, \text{alkylene}$

$(\text{O})_{n''}$

of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms, $-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{CHR}_1)_n-$,
 O

$-\text{CH}(\text{CHR}_1)_n-$, $-\text{CH}=\text{N}-$, $-\text{C}-\text{O}-$, $-\text{C}-\text{S}-$, $-\text{C}-\text{N}(\text{R}_1)-$;
 OH O O O

Z is an alkylene chain containing up to 10 carbon atoms in the principal chain and a total of up to 12 carbon atoms and from 0 to 2 double bonds

each R is a substituent, attached to one of the carbon atoms of Z selected from the group consisting of =O, OR_3 , SR_3 , $\text{N}(\text{R}_2)_2$ and $-\text{COR}_4$;

R_1 is H or CH_3 ;

R_2 is H, lower alkyl, aryl or aralkyl;

R_3 is H, lower alkyl, lower alkanoyl, aryl or aralkyl or an 0-heterocyclic group;

R_4 is OR_2 or $\text{N}(\text{R}_2)_2$;

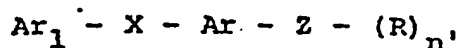
$n = 0$ or 1;

$n' = 1$ to 7; and

$n'' = 0, 1$ or 2.

1

12. A compound of Claim 1 of the formula:



and salts thereof;

5

wherein

Ar_1 is a phenyl or naphthyl group;

Ar is a phenyl group;

$\text{X} = -\text{O}(\text{CHR}_1)_n-, -\text{S}(\text{CHR}_1)_n-, -\text{NR}_2(\text{CHR}_1)_n-, \text{alkylene}$
 $(\text{O})_{n''}$

10

of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms; $-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-, -\text{C}\equiv\text{C}-, -\text{CH}=\text{N}-,$

$-\text{C}-\text{N}(\text{R}_1)-;$
 O

15

Z is alkylene chain containing up to 10 carbon atoms in the principal chain and a total of up to 12 carbon atoms and from 0 to 2 double bonds and the

20

each R is a substituent, attached to one of the carbon atoms of Z selected from the group consisting of $=\text{O}, \text{OR}_3, \text{N}(\text{R}_2)_2$ and $-\text{COR}_4$;

R_1 is H or CH_3 ;

R_2 is H , lower alkyl, aryl or aralkyl;

25

R_3 is H , lower alkyl, lower alkanoyl, aryl or aralkyl and said 0-heterocyclic group is a pyran group or tetrahydropyran group;

R_4 is OR_2 or $\text{N}(\text{R}_2)_2$;

$n = 0$ or 1 ;

$n' = 1$ to 7 ; and

30

$n'' = 0, 1$ or 2 .

35

1 13. The compound according to Claim 1 which is
methyl 3-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoate, methyl
2-[[3-(1-hydroxyhexyl)phenoxy]methyl]benzoate, 3[[3-
5 (1-hydroxyhexyl)phenoxy[methyl]benzamide, methyl-3-[3-
(1-methyl-1-hexenyl)phenoxy]methyl]benzoate, 1-(3-phenoxy-
phenyl)-1-hexanol, 1-(3-benzyloxphenyl)-1-methyl-1-pentanol,
2-(3-hexanoylphenoxy)methyl naphthalene, 2-(3-(1-hydroxy-
hexyl)phenoxy)methyl naphthalene or 2-(3-(1-hydroxyhexyl)-
phenoxymethyl)-1,2,3,4-tetrahydronaphthalene.

10 14. A method of treating inflammatory and
allergic conditions in a mammal by administering to
said mammal an effective amount of a compound of any of
Claims 1-13.

15 15. A process for the production of a compound
as in Claim 1, which includes at least one of the following:

20 (a) condensation of a compound of formula
II and III herein in which X' and X" are $-\text{CH}_2\text{Hal}$, Hal,
OH, CH_2OH , SH or CH_2SH , the nature of X' and X" being
such to permit formation of Z on condensing to a compound
of formula I herein;

25 (b) condensation of compounds of formula II
and III herein in which X' and X" are $-\text{CH}=\text{CH}_2-$, $-\text{C}\equiv\text{CH}$,
or Hal, the nature of X' and X" being such to permit formation
of Z on condensing to a compound of formula I herein;

30 (c) condensing compounds of formulas II and III
herein in which X' and X" are $-\text{CHO}$ or $-\text{NH}_2-$, the nature
of X' and X" being such to permit formation of Z on
condensing to a compound of formula I herein;

35 (d) condensing compounds of formula II and III
herein in which X' and X" are COOH , or NH , the nature
of X' and X" being such to permit formation of Z on con-
densing to a compound of formula I herein;

1 16. The process of Claim 15 where the compounds
of Formula I are:



and salts thereof,

5

wherein

Ar_1 is quinolyl;

Ar is a phenyl, pyridyl or quinolyl ring

$\text{X} = -\text{O}(\text{CHR}_1)_n-, -\text{S}(\text{CHR}_1)_n-, \text{NR}_2(\text{CHR}_1)_n-;$ alkylene
(O)_n

10

of up to 2 carbon atoms in the principal chain and up to
a total of 4 carbon atoms, $-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-, -\text{C}\equiv\text{C}-, -(\text{CHR}_1)_n-,$
O

$-\text{CH}(\text{CHR}_1)_n-, -\text{CH}=\text{N}-, -\text{C}-\text{O}-, -\text{C}-\text{S}-, -\text{C}-\text{N}(\text{R}_1)-;$
OH

15

Z is an alkylene chain containing up to 10
carbon atoms in the principal chain and a total of up to
12 carbon atoms and from 0 to 2 double bonds

each R is a substituent, attached to one of the
carbon atoms of Z selected from the group consisting of
20 $=\text{O}, \text{OR}_3, \text{SR}_3, \text{N}(\text{R}_2)_2$ and $-\text{COR}_4;$

R_1 is H or $\text{CH}_3;$

R_2 is H, lower alkyl, aryl or aralkyl;

R_3 is H, lower alkyl, lower alkanoyl, aryl or

aralkyl;

25

R_4 is OR_2 or $\text{N}(\text{R}_2)_2;$

$n = 0$ or 1;

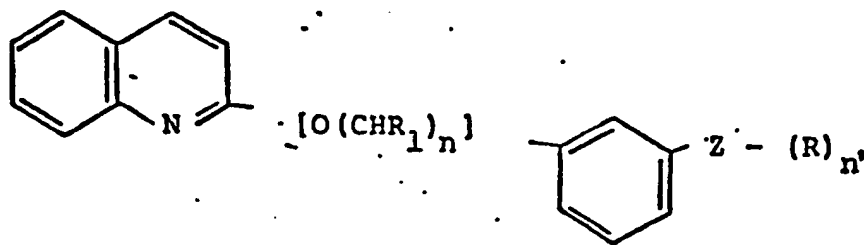
$n' = 1$ to 7; and

$n'' = 0, 1$ or 2.

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17. The process of Claim 15 where the compounds of Formula I are:



and salts thereof,
wherein

Z is an alkylene chain containing up to 10 carbon atoms in the principal chain and a total of up to 12 carbon atoms and from 0 to 2 double bonds;

$n = 0$ or 1 ;

$n' = 1$ to 7 ; and

Each R is a substituent, attached to one of the carbon atoms of Z selected from the group consisting of $=O$, OR_3 , SR_3 , $N(R_2)_2$ and $-COR_4$;

R_1 is H or CH_3 ;

R_2 is H, lower alkyl, aryl or aralkyl;

R_3 is H, lower alkyl, lower alkanoyl, aryl or aralkyl;

R_4 is OH, OR_2 or $N(R_2)_2$;

$n = 0$ or 1 ;

$n' = 1$ to 7 ;

with the proviso that one R is on the carbon atom of Z attached to the phenyl group.

$$Ar_1 - X - Ar - Z - (R)_n.$$

wherein

Ar is a phenyl, pyridyl or quinolyl group;

10

15

z is an alkylene chain containing up to 10 carbon atoms in the principal chain and a total of

each R is a substituent, attached to one of the carbon atoms of Z selected from the group consisting of =O, OR₃, SR₃, N(R₂)₂ and -COR₄;

25

R_3 is H, lower alkyl, lower alkanoyl, aryl or an O-heterocyclic group;

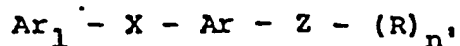
$n = 0$ or 1 ;

$$n'' = 0, 1 \text{ or } 2.$$

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-13-

19. The process of Claim 15 wherein the compounds of Formula I are:



and salts thereof;

wherein

Ar_1 is a phenyl or naphthyl group;

Ar is a phenyl group;

$\text{X} = -\text{O}(\text{CHR}_1)_n-, -\text{S}(\text{CHR}_1)_n-, -\text{NR}_2(\text{CHR}_1)_n-, \text{alkylene}$
 $(\text{O})_{n''}$

of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms; $-\text{C}(\text{R}_1)=\text{C}(\text{R}_1)-, -\text{C}\equiv\text{C}-, -\text{CH}=\text{N}-,$

$-\text{C}-\text{N}(\text{R}_1)-;$
 O

Z is alkylene chain containing up to 10 carbon atoms in the principal chain and a total of up to 12 carbon atoms and from 0 to 2 double bonds and the

each R is a substituent, attached to one of the carbon atoms of Z selected from the group consisting of $=\text{O}, \text{OR}_3, \text{N}(\text{R}_2)_2$ and $-\text{COR}_4$;

R_1 is H or CH_3 ;

R_2 is H , lower alkyl, aryl or aralkyl;

R_3 is H , lower alkyl, lower alkanoyl, aryl or aralkyl and said 0-heterocyclic group is a pyran group or tetrahydropyran group;

R_4 is OR_2 or $\text{N}(\text{R}_2)_2$;

$n = 0$ or 1 ;

$n' = 1$ to 7 ; and

$n'' = 0, 1$ or 2 .

(19)



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report: 26.04.89 Bulletin 89/17(71) Applicant: **USV PHARMACEUTICAL CORPORATION, 1**
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Kinkeldey, Dr. Stockmair, Dr. Schumann, Jakob, Dr.
Bezold, Meister, Hilgers, Dr. Meyer-Plath,
Maximilianstrasse 58, D-8000 München 22 (DE)(54) **Anti-inflammatory/anti-allergic compounds.**

(57) Compounds of the formula:

 $\text{Ar}_1 - \text{X} - \text{Ar} - \text{Z} - (\text{R})_n$ and salts thereof, wherein Ar_1 is a nitrogen, sulfur, oxygen heterocyclic ring or aromatic ring; Ar is a phenyl ring or a nitrogen, oxygen or sulfur heterocyclic ring; Ar and Ar_1 may be fully substituted or less than fully substituted with H, CH_3 , lower alkyl, aryl, aralkyl, halo, hydroxy, lower alkoxy, CF_3 , carboxy, alkylcarboxy, arylcarboxy, alkylcarbalkoxy, alkanoyl, formyl, oxo, nitrilo, amino, aminoalkyl, alkylamine, carbamate, aryloxy, nitro, sulfonyl, sulfonamide, thio, or alkylthio; $\text{X} = -\text{O}(\text{CHR}_1)_n-$, $-\text{S}(\text{CHR}_1)_n-$, $-\text{NR}_2(\text{CHR}_1)_n-$ alkylene

of up to 2 carbon atoms in the principal chain and up to a total of 4 carbon atoms,

 $-\text{C}(\text{R}_1) = \text{G}(\text{R}_1)-$, $-\text{C} = \text{C}-$, $-\text{C}(\text{CHR}_1)_n-$

$$\begin{array}{c} \text{O} \\ || \\ -\text{CH}(\text{CHR}_1)_n-, -\text{CH} = \text{N}-, -\text{C}-\text{O}-, -\text{C}-\text{S}-, \text{or } -\text{C}-\text{N}(\text{R}_1)-; \\ || \quad || \quad || \\ \text{O} \quad \text{O} \quad \text{O} \end{array}$$

OH

 Z is an alkylene chain containing up to 10 carbon atoms in the principal chain and a total of up to 12 carbon atoms and from 0 to 2 double bonds and the said alkylene chain may be attachedto Ar through an oxygen, sulfur or amino nitrogen atom, and when $n' = 2$, one of the R substituents may be halogen on an omega carbon of the alkylene chain Z ;**EP 0 181 568 A3**



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00181568

Application Number

EP 85 11 3830

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
E	EP-A-0 223 368 (AMERICAN HOME PRODUCTS) * example 16 * ---	1 - 19	C 07 D 215/14 C 07 D 213/30 C 07 D 213/79
E	EP-A-0 219 307 (MERCK FROSST) * examples 1 - 11 * ---	1 - 19	C 07 C 43/23 C 07 C 49/76 C 07 D 215/22
E	EP-A-0 206 772 (DUPONT) * tables II, III, etc * ---	1 - 19	C 07 D 213/84 C 07 C 65/21 C 07 C 69/76
E	EP-A-0 206 751 (MERCK FROSST) * tables I, II, III, examples * ---	1 - 19	C 07 C 121/75 C 07 C 47/575 A 61 K 31/47
E	EP-A-0 200 101 (USV) * examples * ---	1 - 19	A 61 K 31/44 A 61 K 31/34 A 61 K 31/38
E	EP-A-0 194 579 (HOECHST) * examples 4a, 6a, 11 * ---	1 - 19	A 61 K 31/085 A 61 K 31/12 -/-
E	EP-A-0 190 722 (USV) * examples 1 - 7, 10 - 16; list page 25 * ---	1 - 19	
E	EP-A-0 173 172 (HOECHST) * pages 11, 12; examples; table II * ---	1 - 19	C 07 D 213/00 C 07 D 215/00 C 07 D 307/00
E	EP-A-0 169 581 (BOEHRINGER) * examples * ---	1 - 19	C 07 D 333/00 C 07 C 43/00
P,X	EP-A-0 153 678 (TENAKE) * table 1 (compounds 1, 5); examples 1, 2, 10, 11; reference example 1 * ---	1 - 19	
P,X	DE-A-3 442 034 (OTSUKA) * examples 6, 18, 19, 37, 44 * --- -/-	1 - 19	
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 19-12-1988	Examiner LEONARD
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P,X	US-A-4 520 199 (KOHN) * examples 1 - 4; table A *	1 - 19	A 61 K 31/19 A 61 K 31/235
P,X	EP-A-0 142 328 (DOW) * examples 1(F), 2, 3, 4(C), 5(E), 5(F), list on pages 19, 20 *	1 - 19	A 61 K 31/165 A 61 K 31/275
X	US-A-4 469 872 (ANDERSON) * examples 1 - 10; table B *	1 - 19	
X	DE-A-3 405 395 (YAMADA) * compounds no. 4 (page 21), 8 (page 23) *	1 - 19	
X	US-A-4 464 533 (KRASS) * column 3, lines 29, 30 *	1 - 19	
X	US-E- 31 624 (DEWHIRST) * whole document, especially example 3 *	1 - 19	
X	EP-A-0 110 405 (USV) * whole document, especially examples *	1 - 19	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	EP-A-0 109 483 (ZOECON) * examples, tables *	1 - 19	
X	FR-A-2 534 582 (KOTOKUKI) * examples; list pages 2 - 4 *	1 - 19	
X	EP-A-0 098 751 (ICI AUSTRALIA) * tables; list pages 6 - 7 *	1 - 19	
X	GB-A-2 119 801 (HOFFMANN) * examples *	1 - 19	
		-/-	
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EUROPEAN SEARCH REPORT

00181568

Application Number

EP 85 11 3830

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X	EP-A-0 086 375 (CELAMERCK) * examples; lists * ---	1 - 19	
X	WO-A-8 204 045 (MAX PLANCK) * compounds on pages 6, 7, 9 * ---	1 - 19	
X	EP-A-0 063 418 (ICI) * examples; tables * ---	1 - 19	
X	DE-A-3 101 544 (HOECHST) * examples; tables * ---	1 - 19	
X	PATENT ABSTRACTS OF JAPAN vol. 6, no. 102 (C-107) (980), 11th June 1982; & JP - A - 57 32279 (MITSUBISHI), 20-02-1982 * whole document * ---	1 - 19	
X	US-A-4 325 729 (REMPFLER) * examples * ---	1 - 19	
X	US-A-4 287 335 (ICHIMURA) * examples; tables * ---	1 - 19	
X	DE-A-3 006 351 (BASF) * examples * ---	1 - 19	
X	EP-A-0 041 476 (CIBA-GEIGY) * examples * ---	1 - 19	
X	EP-A-0 034 349 (TENAKE) * whole document, especially examples * ---	1 - 19	
X	EP-A-0 029 319 (ICI AUSTRALIA) * examples * ---	1 - 19	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
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Application Number

EP 85 11 3830

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X	PATENT ABSTRACTS OF JAPAN vol. 5, no. 8 (C-39) (680), 20th January 1981; JP - A - 13 6265 (KOGYO GIJUTSUIN), 23-10-1980 * formulae I, II *	1 - 19		
X	US-A-4 255 585 (THUILLIER) * examples *	1 - 19		
X	US-A-4 236 912 (JOHNSTON) * examples *	1 - 19		
X	GB-A-2 042 539 (NISSAN) * examples *	1 - 19		
X	GB-A-2 030 131 (TEIJO) * formula VII; examples *	1 - 19		
X	FR-A-2 426 045 (MEIJI) * example 3 *	1 - 19		
X	FR-A-2 417 488 (KUMIAI) * examples *	1 - 19		TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	EP-A-0 003 532 (BYK GULDEN) * examples *	1 - 19		
X	EP-A-0 002 408 (SOCIETE DE RECHERCHES INDUSTRIELLES) * examples, table *	1 - 19		
X	US-A-4 145 354 (MOOKHERGEE) * columns 1, 2, examples 1, 2 *	1 - 19		
X	CH-A- 603 638 (CIBA-GEIGY) * examples *	1 - 19		
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EUROPEAN SEARCH REPORT

00181568₅
Page

Application Number

EP 85 11 3830

DOCUMENTS CONSIDERED TO BE RELEVANT			
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X	DE-A-2 756 771 (CIBA-GEIGY) * claims, examples * ---	1 -19	
X	US-A-4 053 607 (THORNE) * column 9 et seq.; compounds 16 - 32, 39, 42; examples * ---	1 - 19	
X	US-A-4 024 273 (BRENNER) * examples * ---	1 - 19	
X	DE-A-2 647 907 (ELI LILLY) * tables; lists * ---	1 - 19	
X	US-A-4 017 632 (THUILLIER) * examples * ---	1 - 19	
X	DE-A-2 640 430 (SMITHKLINE) * page 2; examples * ---	1 - 19	
X	US-A-3 947 470 (BRENNER) * examples * ---	1 - 19	
X	DE-A-2 522 655 (LABAZ) * examples * ---	1 - 19	
X	DE-A-2 415 867 (MERCK PATENT) * examples * ---	1 - 19	
X	GB-A-1 357 212 (LABAZ) * list, pages 2 - 3, examples * ---	1 - 19	
X	DE-A-2 350 148 (ROUSSEL-UELAF) * whole document, especially examples * ---	1 - 19	
X	US-A-3 793 328 (HESTER) * listed compounds in column 2; examples 2, 3 * ---	1 - 19	
		-/-	
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EUROPEAN SEARCH REPORT

Application Number

EP 85 11 3830

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X	DE-B-1 939 809 (THOMAE) * whole document, especially list on page 9; examples *	1 - 19	
X	SYNTHESIS no. 11, 1976, pages 764 - 765; G. COUDERT et al.: "Synthesis of 2-(2-Oxoalkyl)-quinolines and 4-(2Oxoalkyl)-quinolines" * compounds 6(t), 7(t) *	1 - 19	
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 14, no. 3, 1971, pages 198 - 202; A.R. PATEL et al.: "Some New alpha-Alkylaminomethyl-4-quinolinemethanols" * lists; tables *	1 - 19	
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 15, no. 1, 1972, pages 45 - 48; M. NAKANISHI et al.: "1-Amino-3-phenoxy-2-propanol Derivatives as beta-Adrenergic Blocking Agents" * tables *	1 - 19	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. CL.4)
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